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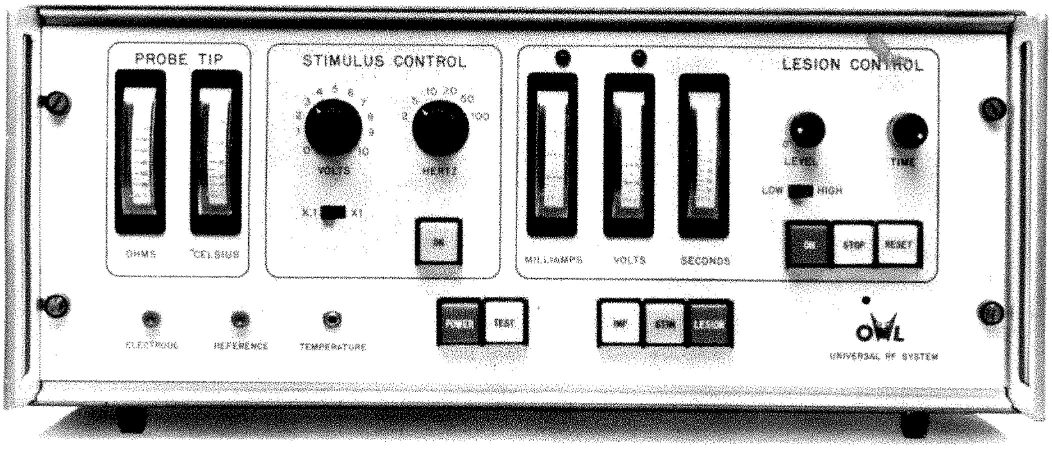

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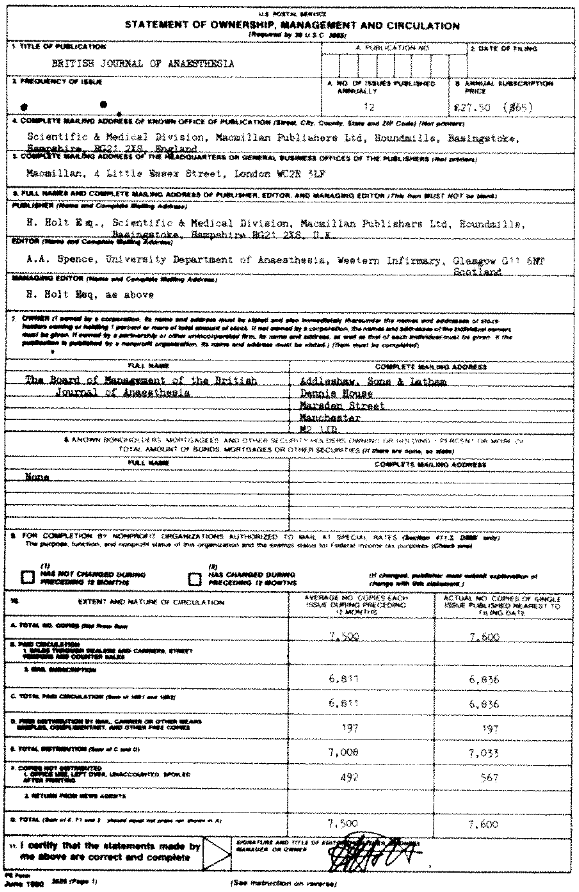

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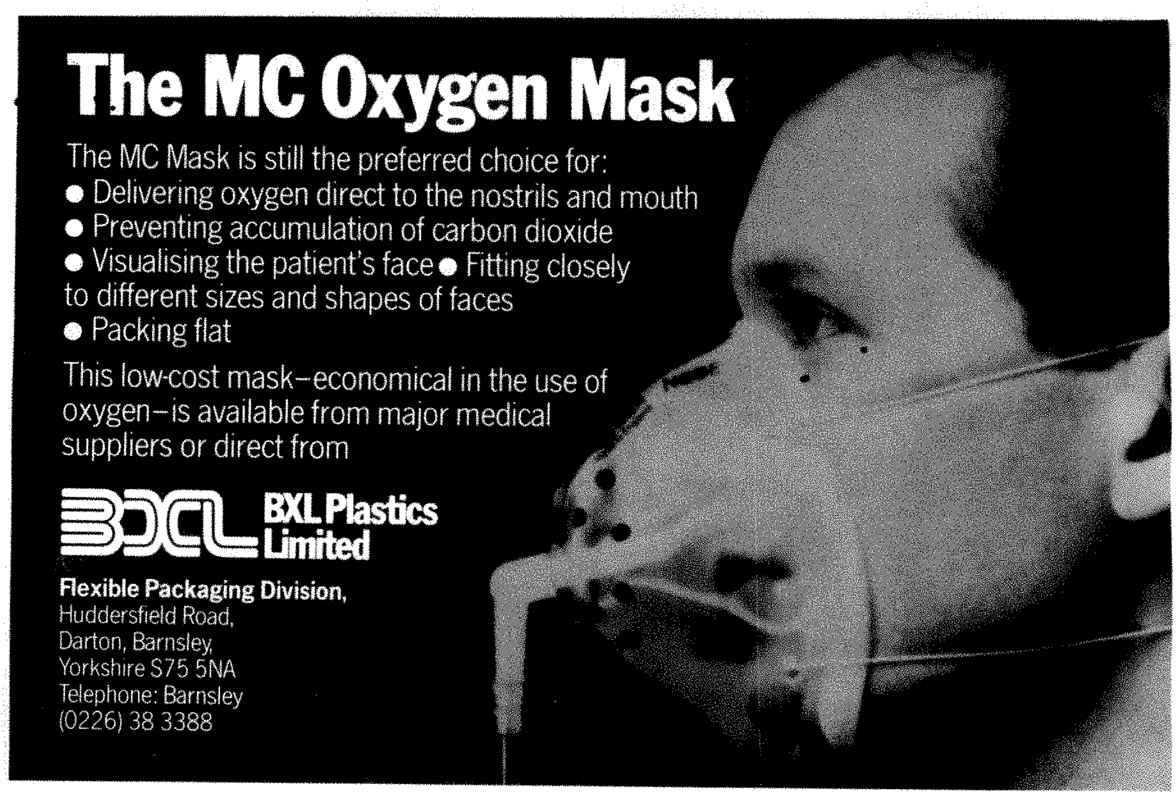
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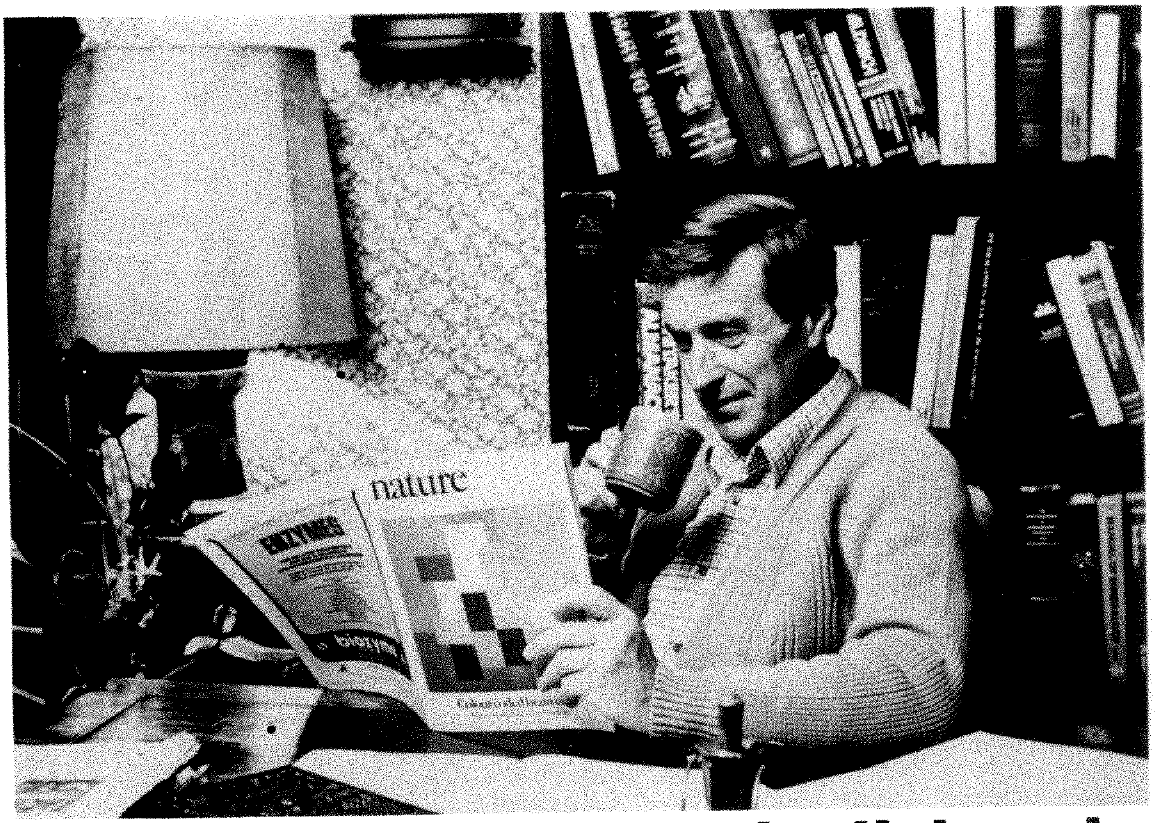

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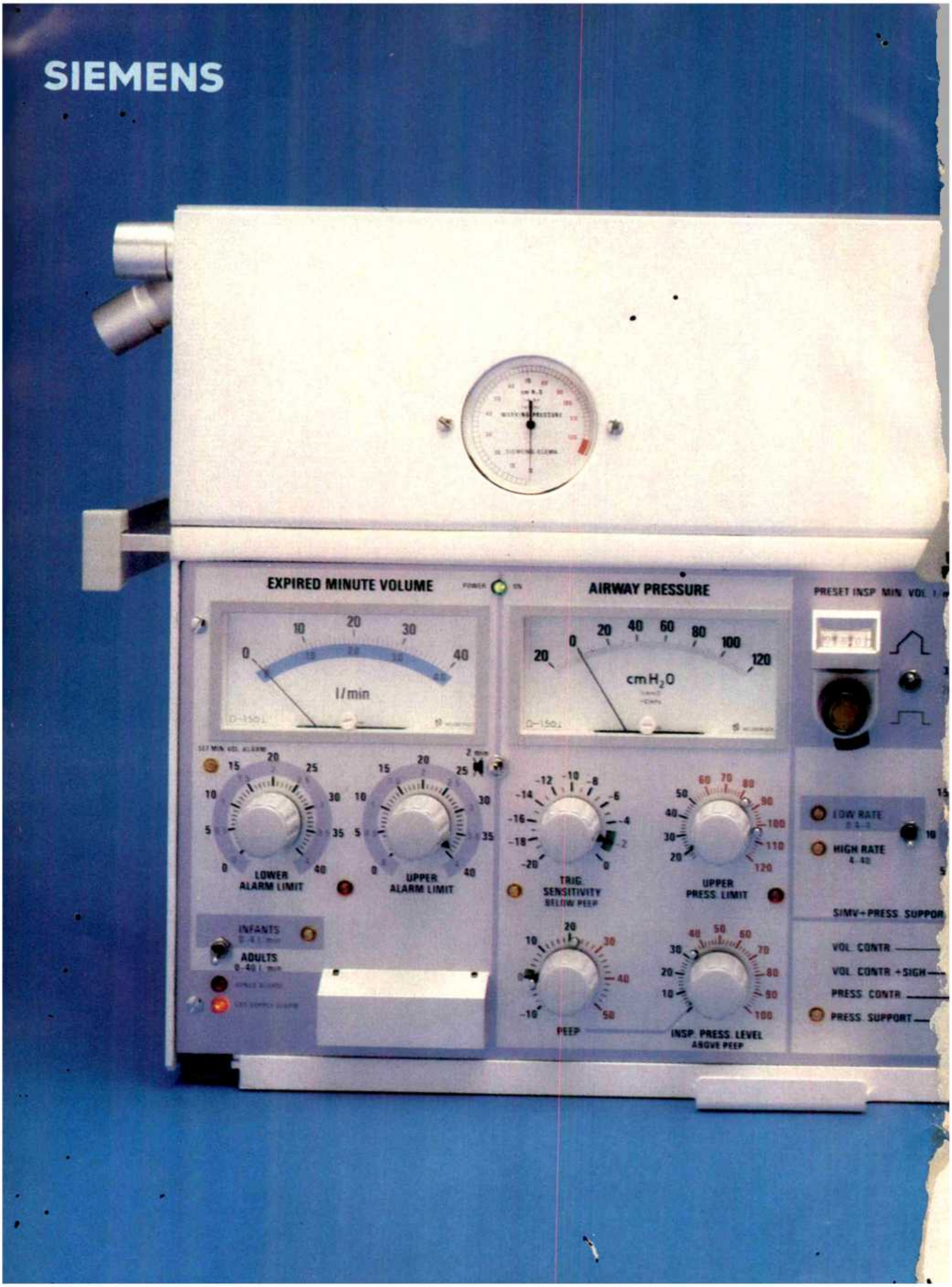
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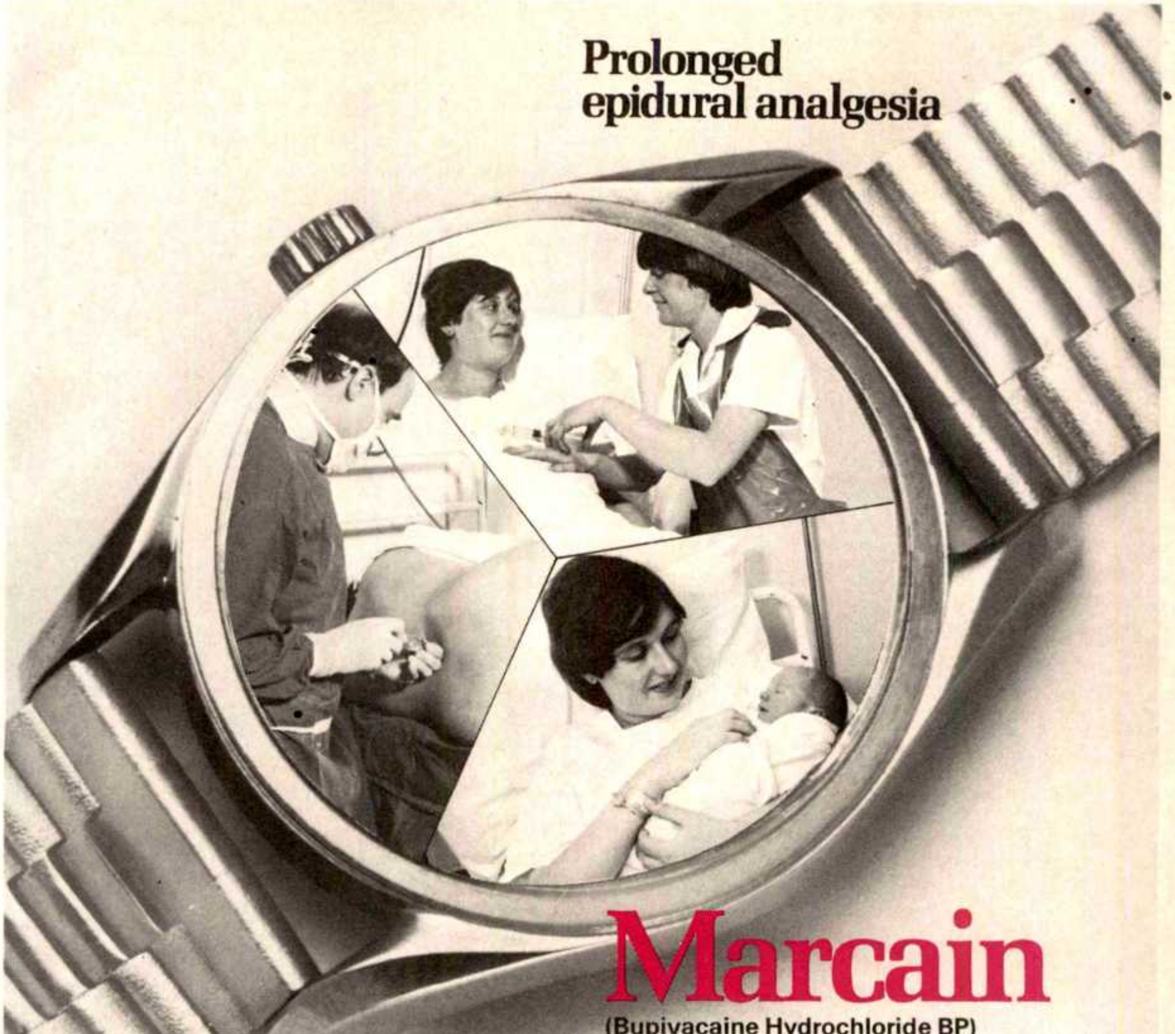

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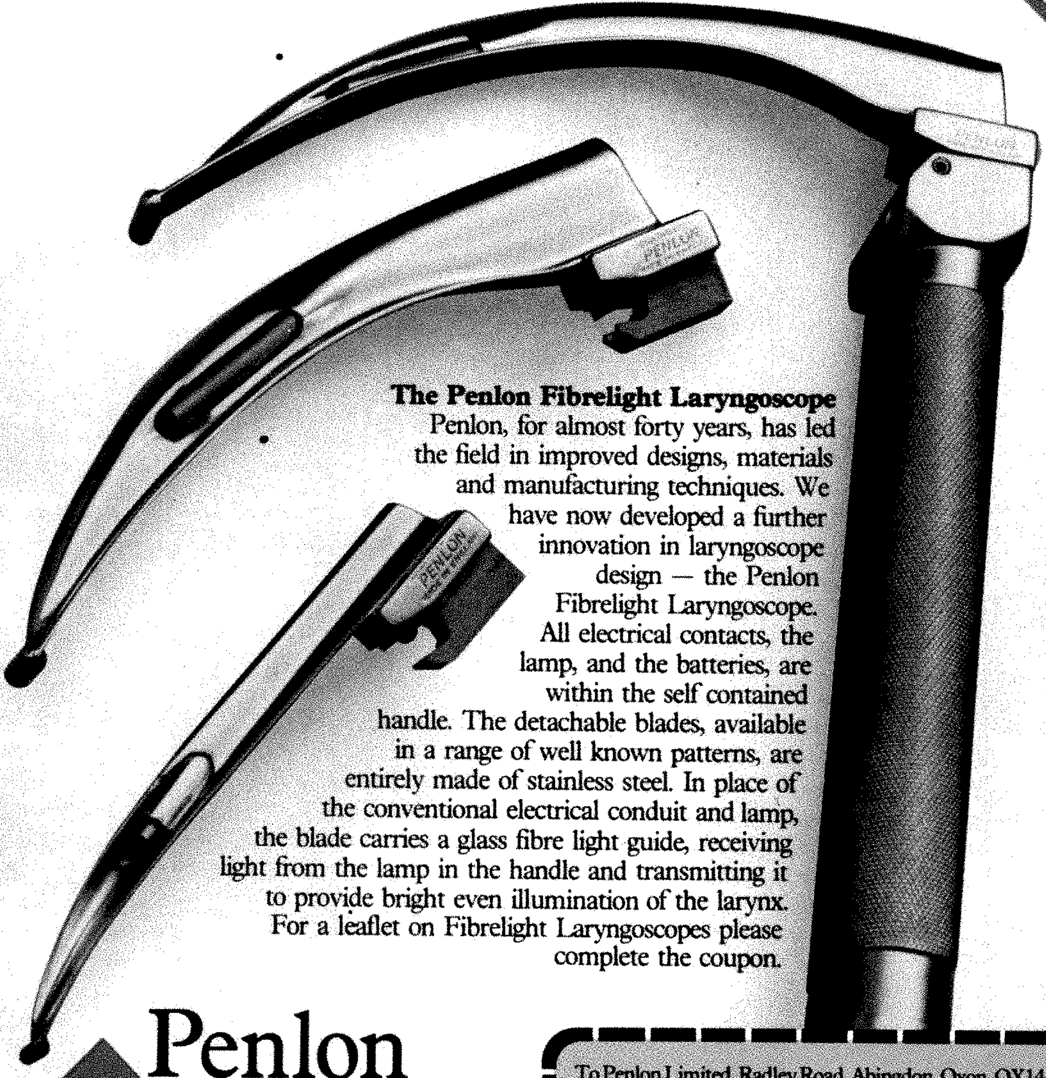

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

THE PROBLEM OF HISTAMINE IN ANAESTHESIA

Ever since the introduction of tubocurarine to clinical practice in the 1940s it has been suggested that the mild hypotension and erythema occasionally associated with its use could be attributed to the release of histamine.

It was not until the early 1970s that reliable and sensitive methods of histamine assay became available. Since that time many drugs used during anaesthesia and surgery have been tested for histamine-releasing properties, both in man and in the experimental animal. Many drugs have a potential for releasing histamine in man, amongst which are the i.v. induction agents propanidid, Althesin, thiopentone and methohexitone; the neuromuscular blocking agents suxamethonium, tubocurarine, alcuronium and pancuronium; the local anaesthetic agent mepivacaine; sedative agents such as flunitrazepam and lorazepam; the analgesics, of which morphine is an example; and the "plasma expanders": polygeline, oxypolygelatin and human albumin.

A symposium* held in Munich in June 1981 allowed world experts in the field of histamine research to meet and discuss the role of histamine release in relation to the adverse reactions which have been observed during anaesthesia and surgery. Such reactions are not only confined to surgery and the administration of anaesthetic agents and plasma "expanders", but also accompany such factors as "stress", trauma and "shock", which may provoke histamine release.

In determining whether histamine release is associated with the adverse response to a particular drug it must be borne in mind that the symptoms and signs may or may not be similar to those elicited by free histamine. In turn, the symptoms and signs will depend upon the amount of histamine released, the individual susceptibility for histamine and the experience and attentiveness of the observer. At the one end of the spectrum may be mild hypotension with or without some cutaneous manifestation and tachycardia, and at the other, profound hypotension, generalized erythema and urticaria and arrhythmias. The mixture of drugs present in the patient at the time of the reaction may enhance, suppress or alter qualitatively, the histamine response. In some instances the possibility exists that the solvent, and not the drug, may be responsible for the adverse reaction. Cremophor El is a particular example of this problem.

The fact that significant histamine release (more than $1\ \mathrm{ng\,ml^{-1}}$) can be detected during standard surgical operations and related to particular surgical events further emphasizes that the anaesthetic agent may not solely be involved with adverse reactions.

We now know that the genetic make-up of an individual and environmental factors are involved in the development of an adverse reaction. The plasma membrane of mast cells may exhibit an altered reactivity to differing stimuli. The concept of "atypical" mast cells, mast cell plasma membranes and mast cell granules has a special relevance in relation to the use of anaesthetic agents dissolved in Cremophor. The H_1 and H_2 receptors situated on the plasma membrane of target cells in many organs such as the heart and brain, the peripheral circulation and the respiratory system are vulnerable to both exogenous and endogenous histamine. Histamine is highly arrhythmogenic and its effect can be potentiated by digitalis and thyroxine. It is also conceivable that anaesthetic drugs may interfere with histamine catabolism and thereby potentiate the effect on the heart. Thus small increases in plasma histamine may cause considerable circulatory reactions in the subject under general anaesthesia. It is also possible that drugs used in anaesthesia may act as H_1 and H_2 receptor antagonists in the central nervous system.

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*"Histamines and Antihistamines in Anaesthesia and Surgery." (Klin. Wochensch., in press.)

Controlled trials in dogs, human volunteers, and patients have indicated that H_1 and H_2 receptor blockade might be a useful premedication against the possible harmful effects of histamine release during anaesthesia and surgery. However, before H_1 and H_2 receptor blockade is advocated as a routine measure the question might be asked: is histamine release in man life-threatening? Most probably, histamine release does not have the same significance in the fit subject as in the individual with high perioperative risks. Indeed, the pharmacological effects of histamine release, particularly vasodilatation and increased cardiac output, might be regarded as a desirable response to what might otherwise be a much more harmful effect of the particular causal agent. We are more familiar with an analogous response, the "flight and fight" mechanism of the autonomic nervous system in response to perceived danger.

The frequency of adverse reactions to substances has a wide variation; for instance where i.v. induction agents are concerned the frequency has been reported as between 1 in 100 and 1 in 30 000, the frequency with those agents which include the solubilizing agent Cremophor El being particularly high. Apart from those agents, which do appear to involve histamine release, the frequency of adverse reactions in clinical practice does not appear to justify the routine premedication with H_1- and H_2-receptor blocking agents. However, when comparisons are made between controlled clinical trials and the reports of adverse reactions in the literature, a much greater frequency of anaphylactoid reactions is encountered in the former. This applies not only to the now discredited formulations (such as polygelin in its original formulation), but also to thiopentone, tubocurarine and morphine (at times in very high doses) (cardiopulmonary by-pass procedures).

Experience indicates that treatment of adverse reactions associated with histamine release should be confined to the conventional administration of oxygen, i.v. fluid replacement and the possible use of adrenaline or isoprenaline and steroids. In the present state of knowledge, the role of H_1- and H_2-receptor blockers would seem to be doubtful, although they may have some place in prophylaxis.

J. A. Thornton

Br. J. Anaesth. (1982), 54, 3

COMPARISON OF I. M. DIAZEPAM AND HYDROXYZINE AS PREMEDICANTS

G. P. HERR, J. T. CONNER, D. SCHEHL AND F. DOREY

SUMMARY

The effectiveness of diazepam as premedication when administered by two different i.m. techniques was compared with hydroxyzine in 84 male and 101 female patients. Variables studied were relief of anxiety, sedation, acceptance by both patient and anaesthetist and pain at the injection site. Diazepam 20 mg in male and diazepam 10 mg in female patients administered by a Z-track injection technique were as effective premedicants as hydroxyzine 100 mg i.m. In men diazepam was as good as hydroxyzine regardless of the injection technique. In women the technique of injection of the diazepam was critical to achieving good results. The Z-track injection method decreased the amount of severe pain on injection in both sexes to levels similar to those achieved with hydroxyzine.

Although the value of diazepam i.v. in premedication has been demonstrated previously (Wender et al., 1977), its efficacy following i.m. injection is more controversial. This paper compares diazepam i.m. with hydroxyzine, a drug known to be effective following i.m. administration (Grady and Rich, 1961). In addition, we investigated whether better results were obtained with standard or with Z-track administration of diazepam.

PATIENTS AND METHODS

One hundred and eighty-five patients, 84 men and 101 women (aged 18–73 yr), in good health and undergoing a variety of operative procedures, with the exception of cardiac surgery and neurosurgery, were studied. None had received a sedative or narcotic drug on the day of study.

In the first part of the study, the drugs were administered by a routine technique in the vastus lateralis using a 1.5-inch, 22-gauge needle. Ordinary care was used in attempting to avoid subcutaneous rather than i.m. injection. A total of 108 patients participated in this section of the study (49 male and 59 female). The drugs (diazepam 10 and 20 mg, and hydroxyzine 100 mg) were given in a double-blind randomized manner. The study was continued until there were a minimum of 14 male and 14 female patients in each group.

All observations before operation were made by a trained nurse observer. Before premedication the patient was asked to evaluate his level of anxiety as negligible, mild, moderate or severe. Five minutes after injection of the drug, his sedation, as compared with the unpremedicated state, was rated as 0 (unchanged), 1+, 2+, 3+, 4+ (improved), or 1−, 2−, 3−, 4− (worsened). The patient was asked to rate anxiety as compared with the unpremedicated state using a similar scale. The evaluation of sedation and relief of anxiety was repeated at 15, 30, 45 and 60 min. Side-effects were noted.

The anaesthetists rated the effect of the drug, without knowledge of its identity, at the time of operation. The overall effect was graded poor (0), fair (1+), good (2+) or excellent (3+). They stated if they would like their patients to receive the medication again. Comments on what they liked or disliked most about the effect of the drug were invited.

Interviews 24 h after operation were made by the nurse observer who was unaware of the identity of the premedicant. The patients were asked to rate the study drug as poor (0), fair (1+), good (2+) or excellent (3+), and if they would like to have the drug again. The injection site was examined for tenderness. This was rated 0 (no pain), 1+, 2+, 3+ (severe pain).

In the second part of the study, diazepam was administered using a 1.5-inch, 22-gauge needle in the vastus lateralis with special attention given to achieving direct i.m. injection. A "Z-track" method was used in which the skin was displaced

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GEORGE P. HERR, M.D.; JAMES T. CONNER, M.D.; DONNA SCHEHL, R.N.; FREDERICK DOREY, PH.D; Department of Anesthesiology, University of California, School of Medicine, Los Angeles, California 90024, U.S.A.

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before insertion of the needle and then allowed to return to its original position after the injection was completed.

A total of 77 patients (35 men and 42 women) participated in this part of the study. Diazepam 10 or 20 mg was given until a minimum of 14 patients of each sex has received this drug. Data were collected as in the first part of the study.

For statistical analyses, raw scores were transformed into ridits based on the hydroxyzine 100 mg data at the corresponding time periods. Analyses were carried out separately for each sex because of the obvious difference in response between the two. We investigated changes in the curves by taking the difference of the ridit sum of the 45- and 60-min points and the 15- and 30-min points. The differences were subjected to a one-way analysis of variance. An appropriate Z statistic was used. Significance was taken at $P < 0.05$.

RESULTS

No statistically significant bias could be demonstrated between the height, weight or age of the patients in any group and the variables studied. No side-effect of any consequence was noted.

Diazepam and hydroxyzine, routine injection

Anxiety (fig. 1, table I). There was no effect of either drug at 15 min; the scores increased with time from 15 min. In men, no significant difference was demonstrated between the effect of either dose of diazepam or hydroxyzine. In women, hydroxyzine was significantly better at relieving anxiety than either dose of diazepam. There was no significant effect of the dose of diazepam in either men or women.

Sedation (table I, fig. 2). The sedation scores, obtained by the nurse, were statistically similar to the results for the relief of anxiety.

Acceptance by the patient 24 h after surgery. No significant difference was found between any of the drugs or doses for either sex.

Acceptance by the physician (table II). The physicians rated diazepam 20 mg higher than diazepam 10 mg. Diazepam 20 mg and hydroxyzine 100 mg were rated equally in men. Hydroxyzine 100 mg was rated the highest in women. The greater dose of diazepam would be used again more frequently than the lower dose.

Diazepam administered by Z-track

Anxiety in men (table I). The relief of anxiety was greater with diazepam 20 mg than with diazepam 10 mg; this trend was not significant. There were no significant differences between the scores with Z-track administration and those with routine i.m. injection.

Anxiety in women (table I, fig. 3). No significant effect of dose was demonstrated. The values for diazepam 10 and 20 mg are plotted in figure 3, with the hydroxyzine data from the first part of the study. There was no significant difference

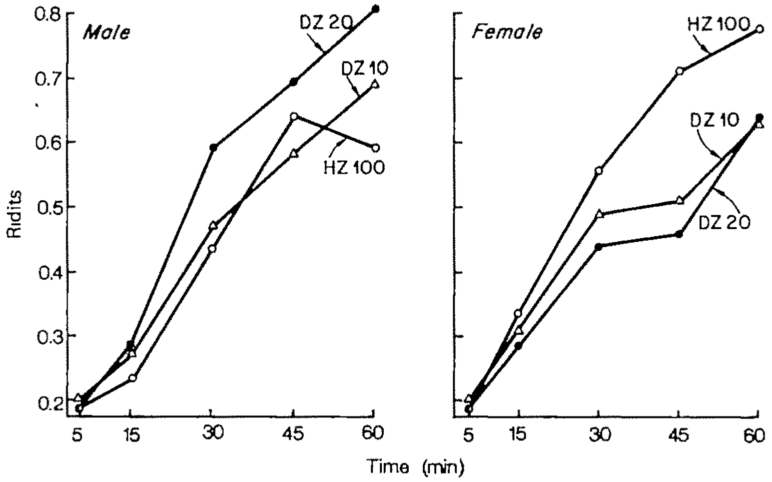

FIG. 1. Mean change in anxiety by sex as scored by the patient compared with the patient's unpremedicated state *v.* time from injection. Routine i.m. injection. Dose in mg: DZ = diazepam; HZ = hydroxyzine.

TABLE I. *Mean anxiety as scored by patients; mean sedation as scored by nurse observer. N = number; M = male; F = female*

	Standard administration						Z-track			
	Diazepam 10 mg		Diazepam 20 mg		Hydroxyzine 100 mg		Diazepam 10 mg		Diazepam 20 mg	
	M	F	M	F	M	F	M	F	M	F
Anxiety (0±4)										
5 min	0.111	0.067	0	0	0	0	0	0	0	0
n	18	15	14	16	17	28	14	15	21	27
15 min	0.333	0.533	0.357	0.5	0.206	0.589	0.321	0.542	0.5	0.944
n	18	15	14	16	17	28	14	12	21	27
30 min	1.36	1.2	1.68	1.06	1.0	1.46	0.857	1.42	1.33	1.54
n	18	15	14	16	17	28	14	13	21	27
45 min	1.64	1.33	2.21	1.19	1.88	2.23	1.32	2.33	1.67	2.48
n	18	15	14	16	17	28	14	15	21	27
60 min	2.23	1.9	2.92	1.92	1.17	2.60	1.43	3.21	2.3	2.75
n	13	10	12	12	10	15	14	12	15	26
Sedation (0±4)										
5 min	0.056	0	0	0	0	0	0	0	0	0
n	18	15	14	16	17	28	14	15	21	27
15 min	0.167	0.20	0.143	0	0	0.214	0	0	0.19	0.33
n	18	15	14	16	17	28	14	15	21	27
30 min	1.11	0.6	0.857	0.5	0.765	0.768	0.143	0.733	0.810	1.07
n	18	15	14	16	17	28	14	15	21	27
45 min	1.22	0.8	1.79	0.812	1.41	1.59	0.643	1.3	1.29	1.96
n	18	15	14	16	17	28	14	15	21	27
60 min	1.71	0.57	2.5	1.17	1.5	2.15	0.714	1.92	1.8	2.39
n	7	7	12	12	8	13	14	12	15	26

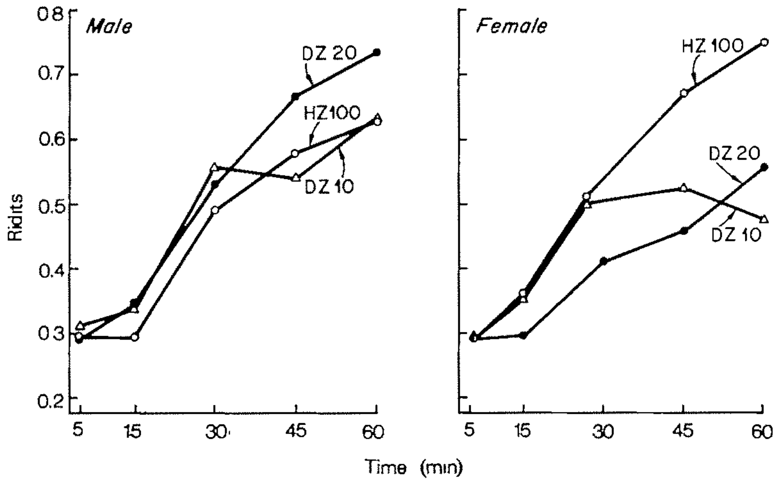

FIG. 2. Mean change in sedation by sex scored by observer compared with the patient's unpremedicated state *v.* time from injection. Routine i.m. injection. Dose in mg: DZ = diazepam; HZ = hydroxyzine.

TABLE II. *Clinician acceptance at surgery. Percentage of patients scored poor (0) to excellent (3); mean weighted score; percentage of anaesthetists who would use drug again (repeat). M = male; F = female*

	Standard administration						Z-track			
	Diazepam 10 mg		Diazepam 20 mg		Hydroxyzine 100 mg		Diazepam 10 mg		Diazepam 20 mg	
	M	F	M	F	M	F	M	F	M	F
Number	18	12	14	13	12	29	13	13	20	24
Poor	44	67	29	54	42	21	54	62	30	50
Fair	33	8	14	38	42	38	38	23	25	25
Good	11	25	57	8	17	31	8	15	30	21
Excellent	11	0	0	0	0	10	0	0	15	4
Mean	0.88	0.58	1.29	0.54	0.75	1.31	0.54	0.54	1.3	0.79
Repeat	50	27	71	38	33	56	25	25	58	40

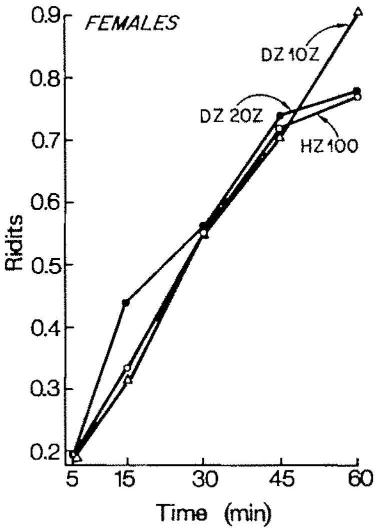

FIG. 3. Mean change in anxiety for females as scored by the patient compared with the patient's unpremedicated state *v.* time from injection. Comparing i.m. injection by Z-track method to routine method. Dose in mg; DZ = diazepam; HZ = hydroxyzine. Z = Z-track method.

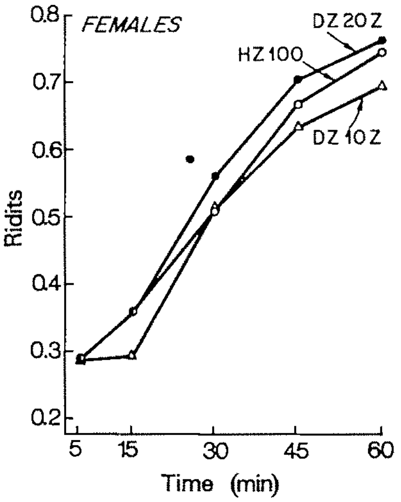

FIG. 4. Mean change in sedation for females scored by the observer compared with the patient's unpremedicated state *v.* time from injection. Comparing i.m. injection by Z-track method to routine method. Dose in mg; DZ = diazepam; HZ = hydroxyzine. Z = Z-track method.

between either dose of diazepam and hydroxyzine.

Sedation (table I, females fig. 4). The sedation scores, obtained by the nurse, were statistically similar to the relief of anxiety curves.

Acceptance by the patient 24 h after surgery. No significant difference was found between the two doses. No significant difference was found for this method of administration and routine i.m. injection in either sex.

Acceptance by the physician (table II). The clinicians rated diazepam 20 mg superior to diazepam 10 mg in men. The Z-track ratings were similar to those for the routine route of administration. For women, the anaesthetists rated all the diazepam doses, regardless of route of administration, similarly.

DISCUSSION

Diazepam has been found to be an effective premedicant when given by mouth or i.v. Its i.m. use is controversial. Early workers suggested that it was quite effective for the relief of anxiety. However, McCaughy and Dundee (1972) obtained better sedation following oral rather than i.m. administration. A further follow-up study (Gamble, Dundee and Assaf, 1975) demonstrated that the blood concentrations following i.m. injection depended on the site of injection, the length of the needle and the experience of the person giving the injection. If clinicians gave the injection in the vastus lateralis muscle, the blood concentrations were only slightly less than those obtained after oral administration. Even so, it was felt that the i.m. injection was too painful and the oral route was preferred. Korttilla and Linnoila (1975) reported a high frequency of pain during the injection of diazepam into the thigh, but concluded that better sedation was obtained after i.m. use, despite the lower blood concentrations. They suggested that this was the result of the more rapid onset of the effect following i.m. administration.

Our clinical impression and that of others (Tornetta, 1965; Haslett and Dundee, 1968) has been that diazepam i.m. can be used effectively as a premedicant. In general, the results of this study support this and, in addition, suggest that there may be a previously unreported difference between the use of i.m. diazepam in men and women.

We chose hydroxyzine as a reference premedication since it provides good relief of anxiety when used in a dose of 100 mg. Its effectiveness has been demonstrated in previous studies (Grady and Rich, 1961; Bizzari et al., 1963) and there have been no questions raised concerning its absorption following administration i.m.

Our results indicate that, in men, diazepam injected in a routine i.m. manner compared favorably with hydroxyzine 100 mg. There was a non-significant effect of dose; the 20-mg dose scored slightly higher than the 10-mg dose, especially in the anaesthetists' opinion. On the whole, however, there was little difference between either of the doses of diazepam and hydroxyzine based on the relief of anxiety, production of sedation, and acceptance by the patient.

The i.m. injection of diazepam using a standard technique led to significantly lower scores for relief of anxiety and sedation than hydroxyzine in women. Indeed, considering these results in female patients alone, i.m. diazepam could not be recommended. Since diazepam is relatively lipid-soluble and water-insoluble (Greenblatt and Shader, 1974), inadvertent injection into adipose tissue could lead to poor uptake. Women have a much larger layer of subcutaneous fat than men and this may predispose to injection into this area rather than into muscle. This anatomical variation is the most likely explanation for the observed results. Gamble, Dundee and Assaf (1975) and Assaf, Dundee and Gamble (1975) did not study i.m. diazepam in males; our results are consistent with their finding of poor uptake in female patients.

Diazepam is known to be irritating when given i.v., an effect of the drug itself and of the vehicle necessary to make it soluble (Graham, Pagano and Katz, 1977). It also causes pain on i.m. injection. In our study, about 50% of patients of both sexes complained of severe pain on routine i.m. injection of 20 mg (table III). This is greater than the 18% frequency of severe pain in males and 39% in females following i.m. hydroxyzine (table III).

TABLE III. *Pain on injection. Percentage of patients rating no pain (0) to severe pain (3); mean weighted score. M = male; F = female*

	Standard administration						Z-track			
	Diazepam 10 mg		Diazepam 20 mg		Hydroxyzine 100 mg		Diazepam 10 mg		Diazepam 20 mg	
	M	F	M	F	M	F	M	F	M	F
Number	16	15	14	16	17	28	13	16	21	27
None	0	13	0	0	0	0	0	0	0	4
Mild	44	20	14	6	71	25	46	31	38	22
Moderate	38	7	36	38	12	36	54	31	33	37
Severe	19	60	50	56	18	39	0	38	29	37
Mean	1.75	2.13	2.36	2.5	1.47	2.14	1.15	2.06	1.9	2.07

In the second part of this study, we revised our technique of injection from the routine i.m. method to a Z-track method. The Z-track method is recommended for the injection of irritating substances. Displacement of the skin before injection disrupts the pathway to the skin from the i.m. site of disposition and prevents leakage of the substance back into the subcutaneous tissue. It is also likely that the traction applied during the displacement of the skin causes compression of the subcutaneous tissue, allowing deeper insertion of the needle. This would aid direct i.m. injection.

Using this different technique of injection, we found that the relief of anxiety and sedation in the female patients were almost identical to that obtained with hydroxyzine 100 mg. The scores for male patients were not improved over those following routine i.m. injection. However, in both men and women there was a decrease in the percentage reporting severe pain on injection (table III). We cannot say whether the Z-track was effective in increasing absorption in men and decreasing pain on injection in both sexes because it prevented leakage of the diazepam back into the subcutaneous tissue or because it encouraged deeper penetration. Quite possibly both mechanisms are valid.

Neither of the drugs, regardless of dose or mode of injection, was outstanding as regards the percentage of either patients or clinicians who would wish the same premedicant again. In clinical practice, these drugs would normally be combined with a narcotic and in a subsequent study (to be published), we show an increase in acceptability with this combination.

We have not compared the effectiveness of i.m. diazepam with that of oral administration. Our results indicate that, properly administered i.m. with a Z-track method, diazepam can provide as effective relief of anxiety, sedation, acceptance by patient and clinician, and absence of severe pain on injection as hydroxyzine 100 mg. Thus, the i.m. route is acceptable where the oral route is not desirable or not available. We also suggest that, while men may get some slight additional effect from diazepam 20 mg, there is no advantage to using more than 10 mg in female patients.

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COMPARAISON ENTRE LE DIAZEPAM ET L'HYDROXYZINE ADMINISTRES EN TANT QUE MEDICATIONS PREOPERATOIRES PAR VOIE INTRAMUSCULAIRE

RESUME

L'efficacité du diazépam lorsqu'il est administré en tant que médication préopératoire par deux techniques différentes intramusculaires, a été comparée à l'hydroxyzine sur 84 malades hommes et sur 101 malades femmes. Parmi les variables étudiés, nous citerons: le soulagement de l'anxiété, la sédation, l'acceptabilité par le patient et par l'anesthésiste, de même que la douleur au lieu de l'injection. Des doses de 20 mg de diazépam ont été administrées aux hommes en suivant une technique d'injection intramusculaire en Z, alors que les femmes n'en recevaient que 10 mg; ces doses ont été aussi efficaces en tant que médication préopératoire que l'hydroxyzine à raison de 100 mg, aussi administrée par voie intramusculaire. Chez les hommes, le diazépam a été aussi efficace que l'hydroxyzine, même sans tenir compte de la technique d'injection. Chez les femmes, la technique d'injection du diazépam a été critique pour obtenir de bons résultats. La méthode d'injection en Z a diminué la quantité de douleur aiguë au moment de l'injection, et ce dans les deux sexes, jusqu'à des niveaux similaires à ceux obtenus avec l'hydroxyzine.

VERGLEICH ZWISCHEN INTRAMUSKULÄREM DAIZEPAM UND HYDROXYZIN ALS CHIRURGISCHE PRÄMEDIKATION

ZUSAMMENFASSUNG

Die Wirksamkeit von Diazepam als Prämedikation, durch zwei verschiedene intramuskuläre Methoden verabreicht, wurde mit Hydroxyzin bei 84 männlichen und 101 weiblechen Patienten verglichen. Die Variablen, die dabei untersucht wurden, waren die Erleichterung von Angstzuständen, Beruhigungsmassnahmen, Annahme durch den Patienten und durch den Anästhetisten, und Schmerzen an der Injektionsstelle. Diazepam 20 mg bei männlichen und Diazepam 10 mg bei weiblichen Patienten, durch eine Z-Bahn-Injektionsmethode verabreicht, erwiesen sich als ebenso wirksam wie intramuskuläres Hydroxyzin 100 mg. Bei Männern erwies sich Diazepam als ebenso wirksam wie Hydroxyzin, ganz gleich, welche Injektionsmethode verwendet wurde. Bei Frauen war die Injektionsmethode für die Erzielung guter Ergebnisse kritisch. Die Z-Bahn-Injektionsmethode führte zu einer Reduktion der schweren Schmerzen zur Zeit der Injektion bei beiden Geschlechtern auf Stufen, die mit denen bei der Injektion von Hydroxyzin vergleichbar waren.

ESTUDIO COMPARATIVO DEL DIAZEPAM Y DE LA HIDROXICINA INTRAMUSCULARES COMO PREMEDICAMENTOS PARA LA INTERVENCION QUIRURJICA

SUMARIO

Se compararon las efectividades relativas del diazepam y de la hidroxicina como premedicamentos, al administrarse mediante dos técnicas intramusculares diferentes, en 84 pacientes masculinos y en 101 femeninos. Las variables estudiadas fueron el alivio de la ansiedad, la sedación, la aceptación por ambos pacientes y por parte del anestesista y el dolor en el lugar de la inyección. 20 mg de diazepan administrados a los pacientes masculinos y 10 mg de diazepan administrados a las pacientes femeninas, mediante una técnica de inyección de rastro en Z, fueron premedicamentos tan efectivos como 100 mg intramusculares de hidroxicina. En lo relativo a los pacientes masculinos, el diazepan fue tan efectivo como la hidroxicina, independientemente de la técnica empleada para la inyección. En lo tocante a las pacientes femeninos, el tipo de técnica usada para la inyección de diazepam fue algo crítico para lograr buenos resultados. El método de inyección de rastro en Z disminuyó el dolor agudo durante la inyección en ambos sexos, a niveles similares a los conseguidos con hidroxicina.

Br. J. Anaesth. (1982), 54, 11

CONTINUOUS SUXAMETHONIUM INFUSION FOR MICROLARYNGEAL SURGERY

J. CARNIE

SUMMARY

The suxamethonium infusion requirements to maintain a 100% neuromuscular block in patients undergoing microlaryngeal surgery were determined. Anaesthesia was maintained with halothane and the neuromuscular block monitored with a peripheral nerve stimulator delivering train-of-four stimuli. Suxamethonium requirements varied directly with time in a linear manner and the onset and recovery time of the block increased with time. No difficulties in recovery were observed when the duration of infusion was less than 1 h, even when the nature of the block had altered to the non-depolarizing type. A good correlation was observed between neuromuscular block as indicated by peripheral nerve stimulation and laryngeal muscle paralysis.

Suxamethonium provides suitable conditions for laryngoscopy (Ali and Savarese, 1976) and for microlaryngeal surgery (Rajagopolan, Foster-Smith and Ramachandran, 1972; Vourc'h, Tannières and Freche, 1979). In particular, sudden patient movement is minimized, resulting in greater safety when instruments such as the carbon dioxide laser are used. The necessity for absolute immobility has been stressed previously (Snow et al., 1974; Vourc'h, Tannières and Freche, 1979).

Continuous suxamethonium infusion has been described on many occasions (Foldes et al., 1952; Churchill-Davidson, Christie and Wise, 1960; Carden and Vest, 1974; Konchigen and Shaker, 1974; Lee, Barnes and Katz, 1978). However, neuromuscular block has not been monitored continuously throughout the entire surgical procedure. Previous studies, involving a lesser degree of neuromuscular blockade, have established that there is poor correlation between the observed twitch response in the hand, and laryngeal paralysis (Bennet, Giesel and Dalal, 1973) or paralysis of the abdominal muscles during abdominal surgery (Crul et al., 1966); 95% twitch depression of the hand muscle response was associated with incomplete cord paralysis (Donlon, Ali and Savarese, 1974).

A study was undertaken to determine the suxamethonium infusion requirements to maintain neuromuscular blockade of 100% twitch suppression and to determine if the use of the peripheral nerve stimulator afforded good control of the block.

METHODS

Sixteen consecutive patients aged 32–71 yr, undergoing elective microlaryngeal surgery for non-malignant conditions were studied. Patients with malignant disease, liver disease and neurological disease were excluded. An appropriate Kleinsasser suspension laryngoscope was used in all operations, and in eight a carbon dioxide laser was used.

Standardized preoperative medication of morphine 5–15 mg and hyoscine was used. Anaesthesia was induced with sodium thiopentone 3–5 mg kg^{-1}, after the i.v. injection of atropine 0.5 mg and pancuronium 1 mg.

The ulnar nerve was stimulated at the wrist using surface electrodes and a Myotest train-of-four nerve stimulator (Biometer, Odense, Denmark) in the continuous mode. The necessary supramaximal stimulus was determined for each patient with the hand optimally positioned. Tetanic stimulation was never used. Train-of-four stimulation aided visual estimation of the evoked thumb response by providing potentially, four distinct movements.

Tracheal intubation using a Portex 5-mm endotracheal tube was facilitated by suxamethonium chloride 1 mg kg^{-1}. Anaesthesia was maintained with halothane 0.5–1% and 33% oxygen in nitrous oxide; the lungs were ventilated mechanically by an AGA pneumatic ventilator

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delivering a tidal volume of 10 ml kg^{-1}, at a frequency of 12 b.p.m.

On reappearance of thumb movement, an i.v. infusion of suxamethonium chloride 2 mg ml^{-1} in 5% dextrose was commenced in the arm opposite to that stimulated. The rate of infusion was regulated to abolish the observed twitch response. Barely visible twitch movement in the hand is reported to indicate 95–98% twitch depression (Lee, 1975a; Ali and Savarese, 1976). If signs of block recovery were absent after 5 min, the infusion rate was reduced. Any patient who had not demonstrated recovery within the next 5 min would have been excluded from the study; however, this did not prove to be necessary. By these means it was hoped to maintain a 100% block without gross error in dosage.

On completion of surgery, the infusion was discontinued and halothane withdrawn. Lignocaine was used to anaesthetize the larynx under direct vision. The tracheal tube was removed when it was judged clinically appropriate and when there was no evidence of any significant residual block (Murphy et al., 1975).

RESULTS

The duration of surgery was 18–70 min (mean 34 min). The total dose of suxamethonium infused varied between 0.5 and 6.9 mg kg^{-1} (mean 2.8), being given over a period of 8–60 min (mean 28). Ten patients received more than 3 mg kg^{-1}. The dose of suxamethonium required to maintain 100% paralysis was found to be linear with respect to time (fig. 1). Using a least-squares regression line constructed from the data, the dose requirement was found to conform to 0.1 mg kg^{-1} min^{-1}, with 95% confidence limits of 0.06–0.14 mg kg^{-1} min^{-1}.

No relationship was observed between the duration of paralysis resulting from the initial dose of suxamethonium at induction and subsequent dosage requirements.

On discontinuing the infusion, a marked fade was observed in the train-of-four evoked twitch

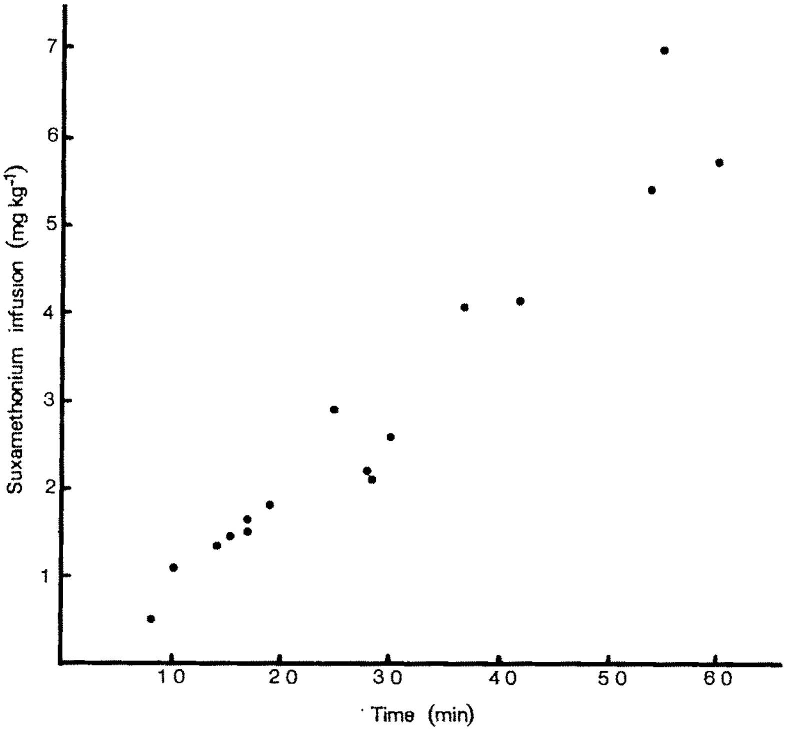

FIG. 1. Each patient's total suxamethonium requirements for the duration of the infusion. The time axis starts from observation of the first recovery twitch response after the initial induction dose of suxamethonium.

responses in eight patients; each had received at least 3 mg kg^{-1} of suxamethonium. The interval between stopping the infusion and tracheal extubation ranged from 3 to 16 min (mean 9). No significant airway or respiratory problems were encountered after operation. During surgery the observed thumb response provided a reliable indication of laryngeal movement. In the majority of patients the surgeon indicated resumption of minimal cord movement immediately before the return of thumb movement.

After a period of time, a difference in speed of onset of recovery and in attaining control of the block was noted. Initially there was a rapid recovery with a corresponding rapidity of control but, as the infusion continued, the converse was noted.

DISCUSSION

In contrast to previous studies (Crul et al., 1966; Bennet, Giesel and Dalal, 1973) good correlation was found between the observed twitch response and muscle paralysis at the site of operation.

A change in behaviour of the neuromuscular block was observed with no overall change in dose required. Several studies using a lesser degree of block or constant dose infusion have demonstrated the changing nature of the resulting neuromuscular block, with two steady-state periods, corresponding to type I and type II block, with a brief period of tachyphylaxis separating the two (Lee, 1975b; Lee, Barnes and Katz, 1978).

The use of train-of-four stimuli was supported by the finding that the majority of patients required a dose in excess of 3 mg kg^{-1}, a dose found in previous studies to be associated with a well established Phase II block (Lee, 1975b; Lee, Barnes and Katz, 1978).

This study also demonstrated a satisfactory speed of recovery of the neuromuscular block when the infusion period was limited to 1 h as shown by Katz and Ryan (1969). The use of such an infusion was not associated with the occurrence of any undesirable clinical features in the patients studied.

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PERFUSION CONTINUE DE SUXAMETHONIUM POUR LES INTERVENTIONS CHIRURGICALES MICROLARYNGIENNES

RESUME

Nous avons déterminé les principes régissant la perfusion de suxaméthonium pour entretenir un blocage neuromusculaire à 100% sur des patients subissant une intervention chirurgicale microlaryngienne. L'anesthésie a été entretenue à l'aide d'halothane et le blocage neuromusculaire a été surveillé à l'aide d'une dispositif électrique de stimulation du nerf périphérique produisant des stimulations par chaîne de quatre. Les exigences du suxaméthonium ont varié d'une manière linéaire directement avec le temps, et le temps compris entre le départ et la récupération du blocage a augmenté avec le temps. On n'a observé aucune difficulté dans la reprise de conscience

lorsque la durée de la perfusion a été inférieure à 1 h, même lorsque la nature du blocage s'était modifiée pour devenir du type non dépolarisant. On a constaté une bonne corrélation entre le blocage neuromusculaire, comme cela a été indiqué par la stimulation du nerf périphérique et la paralysie du muscle laryngien.

KONTINUIERLICHE SUXAMETHONIUMINFUSION BEI KEHLKOPFMIKROCHIRURGIE

ZUSAMMENFASSUNG

Es wurde die Suxamethonium-Infusionsmenge bestimmt, die zur Unterstützung einer 100%-igen neuromuskulären Blockade bei Kehlkopfmikrochirurgie erforderlich wäre. Die Anästhesie wurde mittels Halothan fortgeführt und die neuromuskuläre Blockade wurde mit einem peripheren Nervenstimulator uberwacht, der Viererzug-Reizimpulse lieferte. Die Suxamethoniumforderungen änderten sich direkt in linearer Weise mit der Zeit und das Einsetzen der Blockade und die Erholungszeit stiegen mit der Zeit. Bei einer Infusionsdauer von weniger als einer Stunde wurden keinerlei Schwierigkeiten bei der Erholung beobachtet, selbst dann nicht, als die Blockade sich in eine nicht-depolarisierende gewandelt hatte. Es wurde eine gute Korrelation zwischen der durch periphere Nervenstimulation ausgewiesenen neuromuskulären Blockade und der Kehlkopfmuskellähmung beobachtet.

INFUSION CONTINUA DE SUXAMETONIO PARA LA MICROCIRUJIA LARINGEAL

SUMARIO

Se determinaron los requisitos de la infusión de suxametonio para mantener un bloqueo neuromuscular del 100% en pacientes sometidos a microcirujía de la laringe. La anesthesia se mantuvo con haltano y el bloqueo neuromuscular se vigiló con un estimulador de nervio periférico que entregaba estímulo en trenes de cuatro impulsos. Los requisitos de suxametonio variaron linealmente y de forma directa en el transcurso del tiempo, y el tiempo de inicio y de recuperación del bloqueo aumentaron con el tiempo. No se observaron dificultades en la recuperación cuando la duración de la infusión fue inferior a una hora, incluso cuando la naturaleza del bloqueo se alteró convirtiéndose en el tipo no despolarizante. Se observó una buena correlación entre el bloqueo neuromuscular, tal y como se indicó por la estimulación del nervio periférico y por la parálisis del músculo laringeal.

Br. J. Anaesth. (1982), 54, 15

REMOTE MONITORING BY MASS SPECTROMETRY DURING ANAESTHESIA

Evaluation of a suitable inlet system

G. GORDON, T. BOYD AND R. F. SALAMONSEN

SUMMARY

We describe a three-stage mass spectrometer inlet system suitable for use in operating theatres and evidence of its performance in delay and response times to step changes in oxygen and halothane concentrations. At 55 m and a sampled gas flow of 100 ml min^{-1}, the inlet imposed a delay of 21 s and prolonged the 10–90% response to 310 ms for oxygen and 510 ms for halothane. A linear relationship between inlet length and 10–90% response time at constant sampled gas flow was demonstrated for halothane but not for oxygen. Our results compared with those of other workers support the chosen compromise between practical flexibility and convenience versus maximum speed of response that was adopted in this system design.

Respiratory mass spectrometry is becoming more widely used clinically and although still mainly a research tool, it is able to provide valuable information for patient monitoring. In a busy ward or theatre suite there may be little space and it would be an advantage to place the mass spectrometer (MS) system some distance from the patient. This requires long inlet systems, but permits sequential monitoring of more than one patient.

We have designed an inlet system which conducts sampled gas from the patient's breathing circuit to the analyser in three stages (fig. 1): first stage = a disposable p.t.f.e. sampling cannula (6-mm bore; 1 m long); second stage = a micro-needle valve (S.G.E., Melbourne); third stage = a stainless steel capillary tube (1.54-mm bore; variable length).

An increase in length of the third stage may be expected to prolong the time for the gas front to pass through the inlet system (delay time) and also to establish itself in the ionization chamber (response time). An increase in the sampled gas flow rate would have the opposite effect. The interaction of these two factors has been evaluated in the laboratory and we present the results of this study.

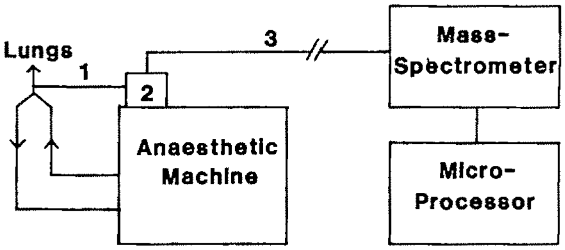

FIG. 1. Schematic diagram of the inlet system. 1 = Disposable p.t.f.e. sampling cannula (1 m); 2 = micro-needle valve mounted on anaesthetic machine; 3 = stainless steel capillary tube (1–55 m).

METHODS

Step changes in oxygen and halothane concentrations were presented to a sampling probe by a gas switch (see Appendix) which was controlled and timed by a computer. This directed the probe into either of two gas streams which had different concentrations of the two agents, then automatically switched the probe back and forth to produce step changes in gas concentration.

All stainless steel components used for the study were prepared by exposure of internal surfaces to 10% phosphoric acid in methanol, 100% methanol and 100% acetone in sequence and subsequently air dried.

By varying the length of the stainless steel capillary tubing and the sampled gas flow we were able to study their effects on the step to 10% delay and the 10–90% response times (as defined in figure 2) of the gases monitored. Using zero

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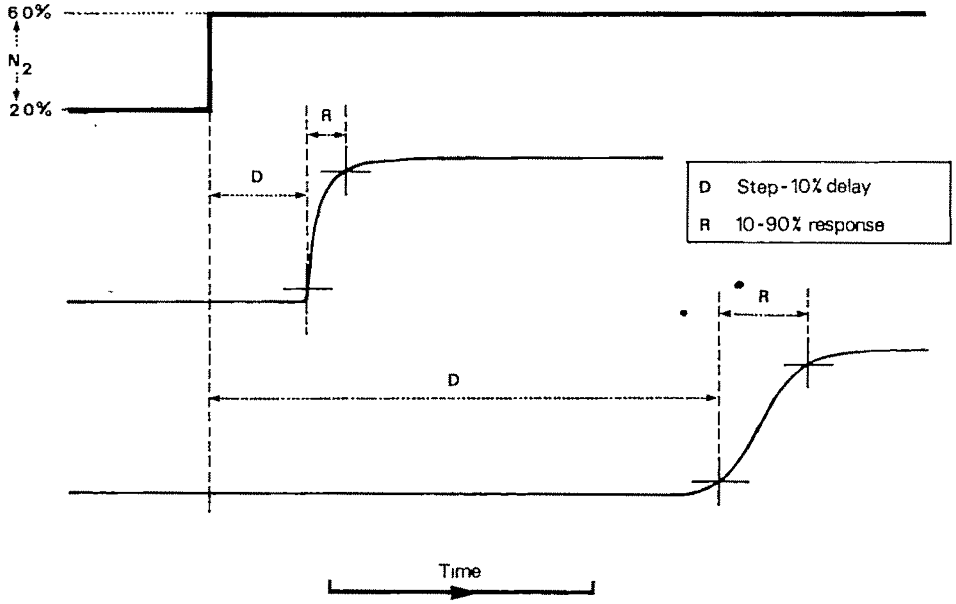

FIG 2. Mass spectrometer response to step changes in gas concentration. The exponential increase applies to short and the sigmoid response to long versions of the inlet. In both cases, response can be assessed in terms of the step-10% delay and 10–90% response times.

deadspace connectors (S.G.E., Melbourne) the stainless steel capillary tubing was lengthened in increments of 11 m to a maximum of 55 m. The sampled gas flow, measured by a high precision rotameter, was increased by adjustment of the inlet needle valve in steps of approximately 25 ml min^{-1} from approximately 10–200 ml min^{-1}. At each length and sampled gas flow, inlet response to step increases *and decreases* in concentrations were measured and the results averaged.

Two ancillary studies were conducted to determine the relative contribution of the micro-needle valve and the p.t.f.e. cannula to inlet response times. First, the response time of the needle valve alone when applied directly to the mass spectrometer was compared with the standard 1-m Gentronic capillary tube at 30 ml min^{-1} (flow rate obtained with the latter). Second, the response of the needle valve alone and of the needle valve with p.t.f.e. cannula was measured at sampled gas flows from 10 to 200 ml min^{-1}.

All measurements were made with an eight-channel mass spectrometer (M.G.A. Centronics, U.K.) interfaced to a Minc 11 microcomputer (Digital Equipment Corporation). Oxygen concentrations were monitored on a single channel but, because of its lower signal to noise ratio, five channels were used for halothane and the results averaged. All channel outputs were modified by the automatic stability control (a facility which expresses the partial pressure of each component as a fraction of the total) to minimize viscosity-induced artefacts in step responses. Delay and response times were then calculated and recorded by the computer.

Statistics. Linear and second-degree polynomial regressions were performed to examine the linearity of relationships between inlet length and 10–90% response time (at constant sampled gas flow) for both halothane and oxygen.

The criterion for alinearity was a significant improvement in fit of the data points to the regression line when the quadratic term was added. The significance of the improvement was tested by an analysis of variance as detailed by Sneddicor and Cockran (1980). The same approach was used to determine whether capillary tube length or square of length was more linearly related to delay time.

RESULTS

Differences in the response of the MS to step increases and decreases in oxygen concentration

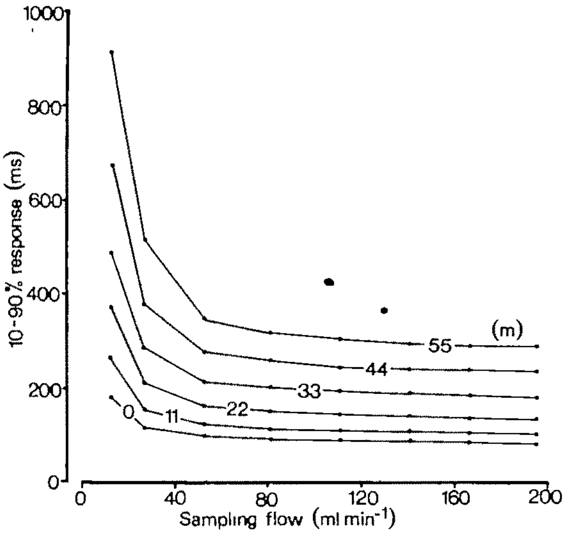

FIG. 3. 10–90% Response to steps in oxygen concentration. Points represent the average of single rise- and fall-time measurements. Lines indicate results for a given inlet length which is inset in metres into each line.

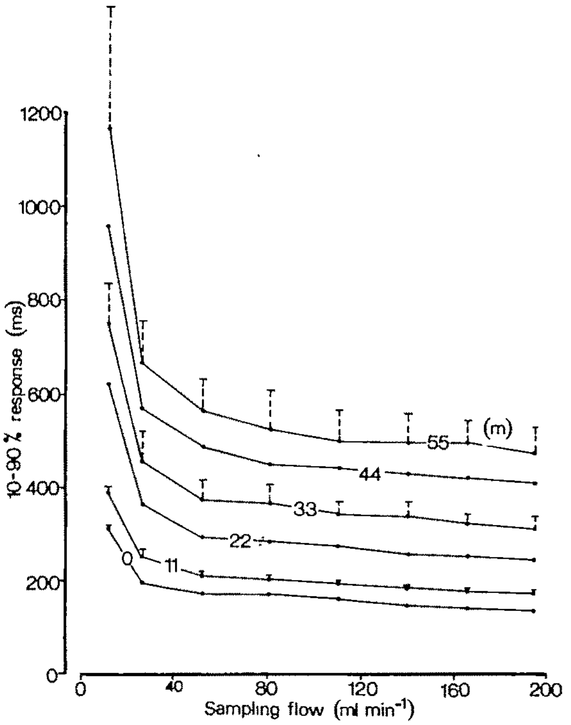

FIG. 4. 10–90% Response to steps in halothane concentration. Points represent the mean of 10 rise- and fall-time measurements. Lines indicate results for a given inlet length which is inset in metres into each line. Vertical interrupted lines give 1 SD ($n = 10$).

(rise and fall times) were slight: usually within 5%, and within 9% in all cases. Greater differences existed for halothane, the fall times being always longer than rise times to a maximum of 18%. The detailed results which follow are reported as the means of individual rise and fall times.

Flow/time relations. Figures 3 and 4 display the 10–90% response times for oxygen and halothane against sampled gas flow rate for various lengths of inlet. Despite the increased variability in the results, the 10–90% response times for halothane are invariably longer than for oxygen. By contrast, delay times for oxygen and halothane were more similar. Although those for halothane were always longer, the differences were not statistically significant. Accordingly, only the results for oxygen are graphed (fig. 5).

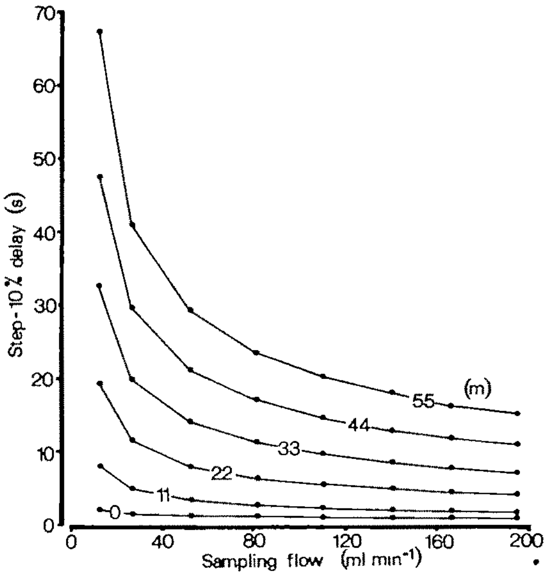

FIG. 5. Step-10% delay times following steps in oxygen concentrations. Points indicate average of delays following single step increases and decreases in oxygen concentration. Lines represent results for a given length which is inset in metres into each line.

Length/time relations. Table I shows that the relationship between inlet length and 10–90% response time is significantly alinear for oxygen but not for halothane over the range of flows tested. Our results (table II) also indicate that, in our inlet system, the step–10% delay does not increase linearly with either inlet length or square

TABLE I. *Regressions of 10–90% response times for oxygen and halothane on inlet length.* O_2 *= oxygen; Hal = halothane;* $\dot{V}s$ *= sampled gas flow.* $P < 0.05$ *= significant deviation from linearity*

	Significance of quadratic term			
	F value		*P*	
$\dot{V}s$ (ml min^{-1})	O_2	Hal.	O_2	Hal.
196	51.7	3.82	<0.01	>0.05
110	45.1	2.50	<0.01	>0.05
11.0	30.3	2.13	<0.01	>0.05

TABLE II. *Regressions of step-10% delay for oxygen on inlet length and square of length. L = inlet length;* L^2 *= inlet length squared;* $\dot{V}s$ *= sampled gas flow.* $P < 0.05$ *= significant deviation from linearity*

	Significance of quadratic term			
	F value		*P*	
$\dot{V}s$ (ml min^{-1})	L	L^2	L	L^2
196	64.0	11.0	<0.01	>0.05
110	82.2	20.9	<0.01	<0.05
11.0	211.7	141.6	<0.01	<0.01

of inlet length, although the alinearity is less with the latter.

Effect of first and second stages. The micro-needle valve and p.t.f.e. cannula (stages 1 and 2 of the inlet) prolong inlet response times. At 30 ml min^{-1} sampled gas flow, the needle valve alone increases 10–90% response from 65 ms (measured with the standard Centronic 1-m capillary tube) to 85 ms. The p.t.f.e. cannula (fig. 6) slows response further, particularly at sampled gas flows of less than 80 ml min^{-1}.

DISCUSSION

With good electronic and vacuum system design, the inlet characteristics largely determine the effective response time of the MS to partial pressure changes of a component in the gas mixture sampled (Buckingham, 1979). During passage through the inlet, the partial pressure gradient of the component is reduced by dispersal into neighbouring gas (Fowler, 1969), absorption into inlet materials (Gillbe, Heneghan and Branthwaite, 1981) or, as for water vapour, adsorption on to cold internal metal surfaces (Fowler, 1958; Stout, Wessel and Paul, 1974).

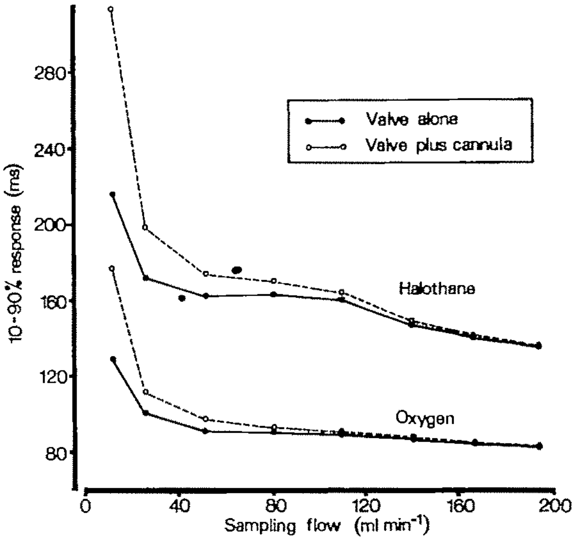

FIG. 6. Response of micro-needle valve and cannula to steps in gas concentration.

Dispersion of a component in surrounding gas occurs in areas of deadspace (particularly if at high pressure), but also during passage down capillary tubes. The latter becomes significant with inlets longer than 4–5 m and relatively more important as inlet lengthens. Goodwin (1979) has given theoretical justification and experimental verification for a lengthening of response time with increasing viscosity of the sampled mixture, decreasing interdiffusion coefficient for the selected component in the mixture and increasing length (but not radius) of the capillary inlet. He also states that the delay time should increase as the square of inlet length.

Our findings are in partial agreement with Goodwin. We found that to a fair approximation, the delay time increases as the square of inlet length. Although a linear relationship was demonstrated between 10–90% response time and inlet length for halothane, this was not the case for oxygen. A possible reason for the discrepancies between the two studies is the more complex geometry of our three-stage inlet as compared with uniform bore of Goodwin's capillary tubes.

Variations in inlet diameters and associated inlet conductances are known to complicate the inlet response to step changes in gas composition (Buckingham, 1979).

The 10–90% response time for halothane agrees with the low diffusion coefficient of organic vapours, but is unlikely to be caused by absorption into inlet materials in our system. Solubility in p.t.f.e. is very low (Fielding, 1978) and is negligible in stainless steel. Adsorption (as for water vapour) remains an alternative explanation. It is possible that surface effects might also account for the more linear relationship between halothane response times and inlet length compared with oxygen.

Stout, Wessel and Paul (1974) suggested a terminal resistance (needle valve) together with a relatively wide-bore tube (1–2 mm) as an alternative to the inlet capillary. Advantages claimed were shorter response and delay times, reduced sensitivity both to water vapour and viscosity changes in sampled gas and greater ease of cleaning. This design concept has been favoured by Glaister and Farncombe (1979) who used either needle valves or minute holes in metal discs for terminal resistances and by Gothard and others (1980) and Gillbe, Heneghan and Branthwaite (1981) who substituted short lengths of narrow-bore capillary tubing at the distal end to achieve a similar effect.

Our approach has been to combine a microneedle valve with a p.t.f.e. capillary tube at the patient end of the inlet. The adjustable needle valve which is mounted on the anaesthetic machine ensures that sampling flow rates can be adjusted for the individual patient irrespective of inlet length. The disposable p.t.f.e. capillary (1 m) makes a clean, convenient and electrically safe connection with the patient circuit. Disadvantages are the complicated geometry of the inlet and the risk of high pressure deadspace distal to the needle which prolong response time as indicated in figure 6. However, the graph also indicates the reduction that can be achieved with faster sampling flows. The clinical importance of these effects is difficult to determine but should assume greater importance as the inlet lengthens and overall response time increases.

Adequate predictions of upper limits of acceptability for inlet length are hampered by the lack of clearly defined limits for delay and response times and sampling flow in different clinical situations. Presumably any significant delay is a disadvantage when gas measurements are incorporated into alarm systems or control mechanisms, but is of much less importance for other monitoring applications provided it is constant and known. Fowler (1969) quotes a maximum 0–90% response time of less than 1 s for low resolution applications such as measurement of slope of the alveolar plateau and less than 100 ms for high-resolution studies such as measurement of cardiogenic oscillations or single-breath deadspace. Davies and Denison (1979) report that cardiogenic oscillations are demonstrated with inlets giving response times of 200–300 ms. Severinghaus (1978) reports response times of up to 700 ms as satisfactory for analysis of inspired and end-tidal concentrations, while many workers accept response times of 300–500 ms (table III). Similarly, although Fowler (1969) specified a maximum sampling flow of 1% minute volume and Davies

TABLE III. *Characteristics of reported inlet systems. A = Severinghaus and Ozanne (1978); B = Glaister and Farncombe (1979); C = Gillbe, Heneghan and Branthwaite (1981); D = Gothard and others (1980); E = Davis and Spence (1979). Cap = short, narrow bore capillary tube; N = nylon; NV = needle valve; TC = terminal constriction; WB = watch bearing*

	Inlet						Response time		
Study	Material	Length (m)	TC	$\dot{V}s$ (ml min^{-1})	Test gas	Delay time (s)	Index (%)	Time (ms)	Instrument
A	N	30	—	180	CO_2	9	0–95	700	?
B	P	30.5	NV	130	N_2	8	0–90	210	MS8
	P	30.5	WB	35	CO_2	10–12	0–90	400	Q701B
C	P	31	Cap.	112	Ar	8.5	0–95	205	MGA200
					CO_2			425	
					He			90	
					SF_6			175	
D	P	30	Cap.	45	CO_2	?	5–95	375	MGA200
E	?	40	?	25	?	30	0–90	500	MGA200

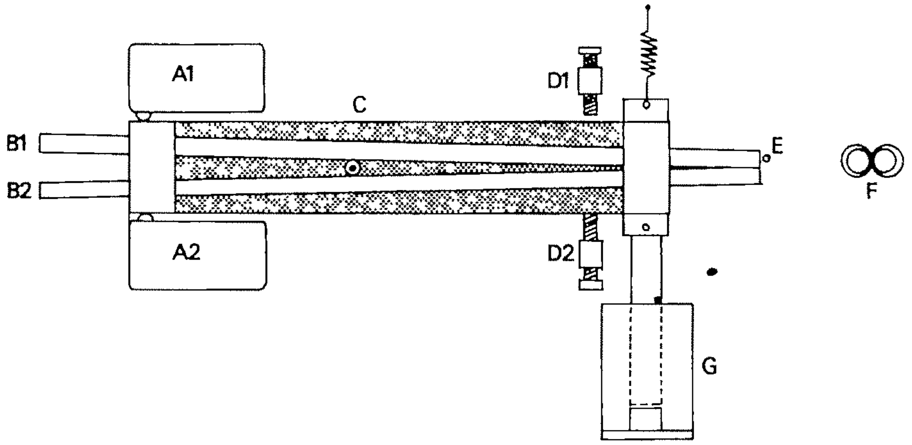

FIG 7. Schematic diagram of gas switching device. A1, A2 = micro switch; B1, B2 = 3-mm stainless steel tubing; C = bearing; D, D2 = adjustable limits; E = sampling cannula; F = cross section of tube orifices which are machined to minimize switching time; G = solenoid which, in conjunction with spring return, actuates the gas switch.

and Denison (1979) a range of 20–50 ml (both unsupported by experimental evidence), a much wider range of sampling flow rates are currently in use (table III). It thus appears that use of inlets up to 50 m or more might be feasible for breath-by-breath analysis of airway gases, but more precise functional specifications are required before definite conclusions can be reached.

APPENDIX

Symbols in text relate to figure 7.

Tubing B1 conducts 2% halothane in dry air mixture while tubing B2 conducts a mixture of 50.1% oxygen, 49.1% nitrogen and 0.8% argon. Position of tube orifices is altered relative to sampling cannula E to provide step changes in oxygen and halothane concentrations. This is achieved by rotating the assembly around the bearing C, by energizing (or de-energizing) the solenoid G. Limits D1 and D2 are adjusted to direct the gas streams to the catheter tip.

Duration of the switching event was the interval between closing of one micro switch and opening of the other under computer control. This was 5±0.5 ms.

ACKNOWLEDGEMENTS

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SURVEILLANCE TELECOMMANDEE PAR SPECTROMETRIE DE MASSE EN COURS D'ANESTHESIE

Evaluation d'un système d'admission approprié

RESUME

Nous décrivons un système d'admission du spectromètre de masse à trois étapes qui est adapté pour utilisation dans les salles d'opération, ainsi que des preuves de son rendement en périodes de délai et de réponse afin de mesurer les modifications des concentrations d'oxygène et d'halothane. A 55 m et un flux de gaz échantillonné de 100 ml min^{-1}, l'admission imposait un délai de 21 s et prolongeait la réponse 10–90% jusqu'à 310 ms pour l'oxygène et à 510 ms pour l'halothane. Un rapport linéaire entre la longueur d'admission et le temps de réponse 10–90% pour un flux de gaz échantillonné constant a été démontré pour l'halothane mais pas pour l'oxygène. Nos résultats comparés avec ceux d'autres chercheurs viennent confirmer le compromis choisi entre la flexibilité pratique et la commodité vis-à-vis de la vitesse de résponse maximale qui a été adopté dans la conception de ce système.

FERNMESSUNG DURCH MASSENSPEKTROMETRIE WÄHREND DER NARKOSE

Beurteilung eines geeigneten Zuflusssystems

ZUSAMMENFASSUNG

Wir beschreiben ein dreistufiges Massenspektrometer-Zuflusssystem für Operationssäle und dessen Leistungen in Verzögerungs- und Reaktionszeiten auf stufenweise Veränderungen bei den Sauerstoff- und Halothankonzentrationen. Bei 55 m und einem Probengasstrom von 100 ml min^{-1} bewirkte der Zufluss eine Verzögerung von 21 s und verlängerte die 10–90% Reaktion auf 310 ms für Sauerstoff und auf 510 ms für Halothan. Ein lineares Verhältnis zwischen Zuflusslänge und 10–90% Reaktionszeit bei konstantem Probengasstrom wurde für Halothan, nicht aber für Sauerstoff demonstriert. Unsere Resultate im Vergleich mit anderen Arbeiten unterstützen den gewählten Kompromiss zwischen praktischer Flexibilität und Bequemlichkeit einerseits und maximaler Reaktionsgeschwindigkeit andererseits, wie er in dem Design für dieses System verwendet wurde.

VIGILANCIA REMOTA POR ESPECTROMETRIA DE MASA DURANTE LA ANESTESIA

Evaluación de un sistema de admisión apropiado

SUMARIA

Describemos un sistema de admisión de un espectrómetro de masa en tres etapas apropiado para el uso en salas de operaciones y pruebas de su rendimiento en tiempos de retardo y de respuesta en la medición de las modificaciones de concentración del oxígeno y del halotano. En 55 m y con un flujo de gas probado de 100 ml min^{-1}, la admisión impuso una demora de 21 s y extendió la respuesta 10–90% hasta 310 ms para el oxígeno y hasta 510 ms para el halotano. Una relación linear entre el largo de admisión y el tiempo de respuesta 10–90%, con un flujo de gas probado constante, se estableció para el halotano, pero no así para el oxígeno. Nuestros resultados comparados con los de otros trabajadores apoyan el compromiso escogido entre la flexibilidad práctica y la conveniencia en comparación con la velocidad máxima de la respuesta, el que fue adoptado para el diseño del sistema.

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INFLUENCE OF EXTRADURAL MORPHINE ON THE ADRENOCORTICAL AND HYPERGLYCAEMIC RESPONSE TO SURGERY

P. CHRISTENSEN, M. R. BRANDT, J. REM AND H. KEHLET

SUMMARY

Plasma cortisol and glucose concentrations were measured repeatedly from before the induction of anaesthesia until 9 h after skin incision in 36 patients undergoing abdominal hysterectomy. Twelve patients received general anaesthesia (halothane), and systemic opiates for postoperative pain; a further 12 patients underwent continuous extradural analgesia with a local anaesthetic agent (bupivacaine) and in the remaining 12 patients general anaesthesia (halothane) plus extradural morphine (4 mg before skin incision and an additional 4 mg at skin closure) were used. Patients receiving extradural morphine or bupivacaine were free of pain. The physiological cortisol and glucose response to surgery was blocked by the extradural analgesia with bupivacaine. Extradural morphine did not modify the initial increase in plasma cortisol and glucose concentrations during surgery, but suppressed the hyperglycaemic and cortisol response following surgery when compared with the general anaesthesia group receiving systemic opiates. However, cortisol and glucose concentrations were greater after operation in patients receiving extradural morphine compared with extradural bupivacaine, suggesting that the endocrine metabolic response to surgery is predominantly released by neurogenic stimuli other than pain stimuli involving opiate receptor-dependent nociceptive pathways.

Surgical trauma induces an endocrine metabolic response with an increase in the secretion of cortisol and catecholamines, and metabolic changes such as hyperglycaemia, lipolysis and negative nitrogen balance. The mechanisms involved are primarily neurogenic as a predominant part of the stress response can be prevented by neurogenic blockade with extradural analgesia (Kehlet, Brandt and Rem, 1980). However, the role of pain stimuli *v.* other neurogenic stimuli in releasing the stress response has not been elucidated completely (Kehlet, 1981). Since the extradural administration of opiates is effective in alleviating pain after operation (Behar et al., 1979; Bromage, Camporesi and Chestnut, 1980; Magora et al., 1980) without concomitant sympathetic blockade (Cousins et al., 1979; Bromage, Camporesi and Chestnut, 1980), we have studied the influence of extradural morphine on the adrenocortical and hyperglycaemic response to lower abdominal surgery and compared the effects with those of general anaesthesia with the systemic administration of opiates and with extradural analgesia using a local anaesthetic agent.

PATIENTS AND METHODS

Thirty-six otherwise healthy premenopausal women, undergoing elective abdominal hysterectomy for menorrhagia or cancer of the uterus (stage 0–1), were included in the study. Informed consent was obtained from all patients. Twelve patients (group A) received general anaesthesia with halothane in nitrous oxide in oxygen and i.m. meperidine or ketobemidone for postoperative analgesia and 12 patients (group B) had surgery performed during extradural analgesia (0.5% bupivacaine 25 ml without adrenaline) without general anaesthesia as described previously (Engquist et al., 1977). Analgesia extended from T4 to S5 before skin incision and was maintained at this level throughout the study. A third goup (C) had general anaesthesia with halothane in nitrous oxide in oxygen similar to group A, and in addition received morphine 4 mg (dissolved in 25 ml of saline) into the extradural space about 30 min before skin incision and an additional 4 mg

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(dissolved in 10 ml of saline) at skin closure. Morphine was thus administered in the same fluid volume as in group B. All patients in groups B and C were calm and most were drowsy following surgery and were apparently free of pain since none complained of pain or requested analgesics when questioned specifically at the time of each blood sample. Patients in group A received a standard analgesic regimen with 50–100 mg of meperidine or ketobemidone 25–37.5 mg every 4 h following surgery. Although pain scoring was not carried out these patients were never totally free of pain during the period of investigation, but complained intermittently.

Groups were comparable ($P > 0.05$) with regard to age (40 ± 2 yr, 37 ± 1 yr, and 41 ± 2 yr) and duration of surgery (89 ± 6 min, 85 ± 6 min, and 92 ± 6 min) in groups A, B and C, respectively (mean ± SEM). Blood loss was less than 500 ml in all patients and was replaced by isotonic saline 2.5 ml/ml blood. No blood transfusion was administered. In addition the patients received isotonic saline 10–15 ml kg^{-1} h^{-1} for the first 2 h and thereafter 1–2 ml kg^{-1} h^{-1}.

Venous blood samples for the measurement of the concentrations of cortisol and glucose were taken from a central catheter 30 and 15 min before induction of general anaesthesia or extradural analgesia with bupivacaine, at skin incision and 0.5, 1, 2, 3, 4, 6 and 9 h later. Plasma cortisol concentration was measured by a competitive protein binding technique (Kehlet, Binder and Engbæk, 1974) and plasma glucose concentration by a routine glucose oxidase method.

Statistical analyses were made by the Kruskal–Wallis test, intergroup variation by Mann–Whitney's rank sum test and intragroup variation by Pratt's test. P values less than 0.05 were considered significant.

RESULTS

The results are summarized in figures 1 and 2.

Plasma cortisol (fig. 1)

Plasma cortisol concentration increased significantly 30 min after skin incision and remained increased ($P < 0.05$) throughout the study in group A. Patients receiving extradural analgesia (group B) showed no significant changes in plasma cortisol concentration except for a decrease at skin incision and 30 min later. Patients receiving general anaesthesia plus extradural morphine (group C) showed significant increases in plasma cortisol concentration from skin incision until 2 h later, after which they had decreased to values similar to those obtained

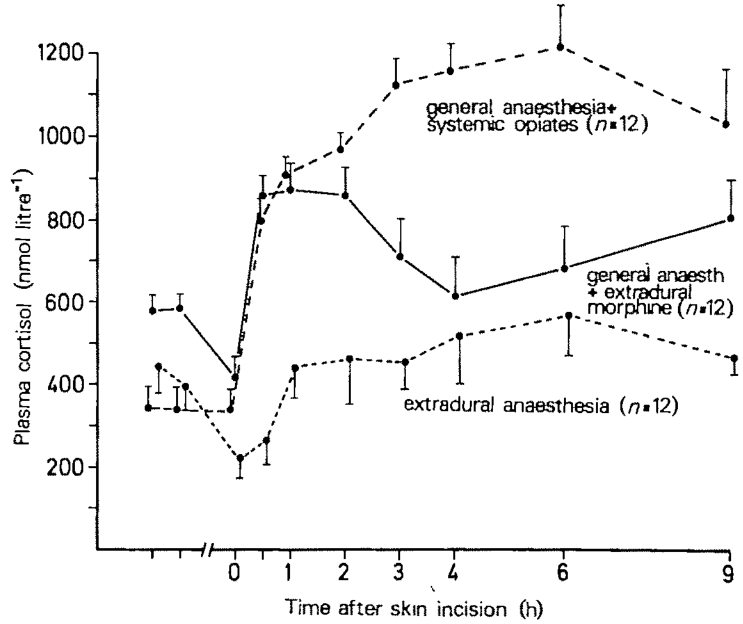

FIG. 1. Influence of extradural morphine on the response of plasma cortisol concentration to abdominal hysterectomy. Mean values ± SEM.

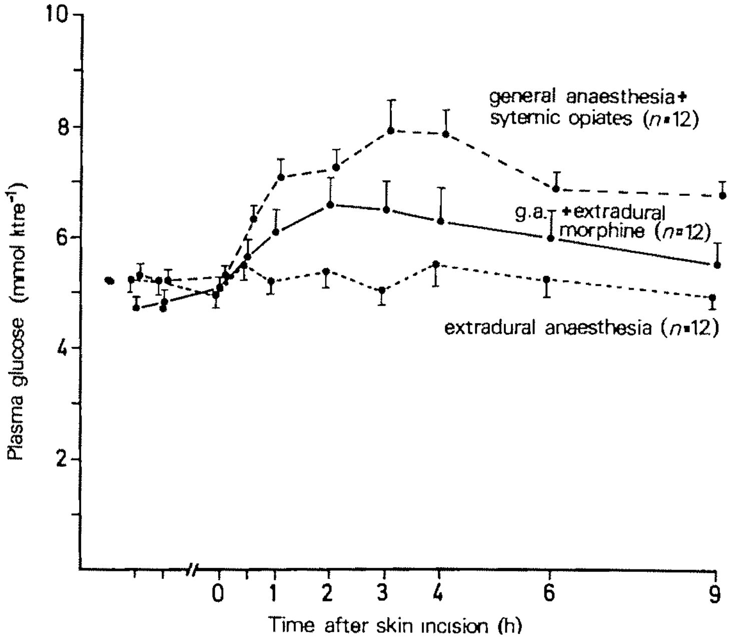

FIG. 2. Influence of extradural morphine on the response of plasma glucose concentration to surgery. Mean values ± SEM.

before operation, by 4 h after skin incision. Later in the postoperative period the plasma cortisol concentration increased again, being significantly greater at 9 h after skin incision compared with the values before operation.

Plasma cortisol concentration was significantly greater in group A from 30 min after skin incision and throughout the study compared with group B. Cortisol values in group A were significantly greater 3, 4 and 6 h after skin incision, when compared with group C. Cortisol concentrations in group B were significantly smaller at skin incision and in the following 2 h and again 9 h after skin incision, when compared with group C.

Plasma glucose (fig. 2)

Plasma glucose concentration increased significantly in group A after skin incision and remained increased ($P<0.05$) throughout the study. Patients receiving extradural analgesia (group B) showed no significant changes. In the patients receiving general anaesthesia plus extradural morphine (C) there was a significant increase in plasma glucose concentration from skin incision and throughout the study.

Glucose concentrations in group A were significantly greater from 30 min after skin incision and throughout the study when compared with group B, and at 3, 4 and 9 h after skin incision in comparison with group C. Glucose concentrations were significantly smaller in group B at 1 and 3 h after skin incision when compared with group C.

DISCUSSION

Afferent neurogenic stimuli from the surgical area are of major importance in mediating the endocrine metabolic response to surgery (Kehlet, Brandt and Rem, 1980), but the relative role of pain stimuli *v.* other neurogenic stimuli is controversial (Kehlet, 1981). Opiate receptors have been demonstrated in the spinal cord (Pert, Kuhar and Snyder, 1976) and opiates inhibit nociceptive pathways in the spinal cord but not the proprioceptive or sympathetic pathways (Calvillo, Henry and Neuman, 1974; Kitahata and Collins, 1981). Clinical studies have shown that the intrathecal or extradural administration of opiates produces an analgesic action without autonomic depression (Behar et al., 1979; Cousins et al., 1979; Bromage, Camporesi and Chestnut, 1980). Therefore the use of extradural morphine represents a method of elucidating the role of nociceptive pathways in mediating the endocrine metabolic response to surgery.

The main finding of our study is that those pain stimuli involving opiate receptor-dependent nociceptive pathways have only a partial role since the alleviation of pain by extradural morphine did not modify the initial increase in plasma cortisol and glucose concentrations occurring during surgery, but did partially inhibit the increased concentrations following operation. This is in accordance with observations of ourselves and others, that surgery cannot be performed during extradural morphine analgesia alone, probably because the stimuli may override the inhibitory action of morphine and because of afferent stimuli through other neurogenic pathways.

It could be argued that the doses of opiate used were insufficient to depress the neurogenic pathways, since other studies have shown that very high doses of opiates administered systemically can block the cortisol and glucose response to surgery (Brandt et al., 1978; Hall et al., 1978). However, in these studies with high-dose opiates the depressant action is probably at the hypothalamic level, in contrast to a spinal and probably segmental action during extradural administration (Bromage, Camporesi and Chestnut, 1980).

Similarly, unblocked nociceptive pathways from the operation site might have been responsible for the increase in plasma glucose and cortisol concentrations under extradural morphine analgesia, but this is unlikely since none of these patients complained of pain when questioned on numerous occasions in the period after operation. Thus, although pain scoring was not performed, we believe that the patients receiving extradural morphine had no more pain after operation than the patients receiving extradural bupivacaine. This was in contrast to the patients receiving a standard analgesic regimen with systemic opiates, from whom there were intermittent complaints of pain. We have no data for the extent of the analgesia, but it probably involved S5–T4, since morphine was administered in a fluid volume, in a manner similar to the administration to the group of patients receiving bupivacaine which did result in analgesia from S5 to T4.

Our finding that pain stimuli play only a partial role in releasing the endocrine metabolic response following surgery supports previous observations made during extradural analgesia with local analgesics where cortisol changes could not be blocked by alleviation of pain alone (Lush et al., 1972; Engquist et al., 1977), unless the afferent blockade included both somatic and all autonomic pathways (Engquist et al., 1977).

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INFLUENCE DE LA MORPHINE EXTRADURALE SUR LA REACTION CORTICO-SURRENALE ET HYPERGLYCEMIQUE A TOUTE INTERVENTION CHIRURGICALE

RESUME

Les concentrations de cortisol et de glucose dans le plasma ont été mesurées plusieurs fois—entre la période qui a précédé l'induction de l'anesthésie et jusqu'à 9h après l'incision de la peau—sur 36 patientes devant subir une hystérectomie par

voie abdominale. Douze d'entre elles ont été soumises à une anesthésie générale (halothane) et à des opiacés systémiques pour calmer la douleur postopératoire; douze autres patientes ont reçu une analgésie extradurale continue à l'aide d'un agent anesthésiant local (bupivacaïne) alors que les douze dernières ont été soumises à une anesthésie générale (halothane) plus morphine extradurale (à raison de 4 mg avant l'incision de la peau et de 4 mg supplémentaires au moment de la suture de la peau). Les patientes ayant reçu extraduralement de la morphine ou de la bupivacaïne n'ont ressenti aucune douleur. La réaction physiologique du cortisol et de la glucose à l'intervention chirurgicale a été bloquée par l'analgésie extradurale à la bupivacaïne. La morphine extradurale n'a pas modifié l'augmentation initiale des concentrations de cortisol et de glucose dans le plasma pendant l'intervention chirurgicale, mais elle a supprimé la réaction postopératoire à l'hyperglycémie et au cortisol, ceci par comparaison au groupe soumis à une anesthésie générale et à des opiacés systémiques. Cependant, les concentrations de cortisol et de glucose après l'opération ont été plus fortes chez les patientes auxquelles on avait administré de la morphine extradurale que chez celles ayant reçu de la bupivacaïne extradurale, ce qui laisse penser que la réaction endocrine métabolique à la chirurgie est surtout due aux stimulants neurogéniques autres que les stimulants de la douleur mettant en cause, en ce qui concerne les opiacés, les voies d'accès nociceptives dépendants des récepteurs.

EINFLUSS VON EXTRADURALEM MORPHIUM AUF DIE ADRENOKORTIKALE UND HYPERGLYKÄMISCHE REAKTION AUF DIE CHIRURGIE

ZUSAMMENFASSUNG

Plasmakortisol und Glukosekonzentrationen wurden schon vor der Einleitung der Anästhesie bis 9 Stunden nach dem ersten Einschnitt wiederholt bei 36 Patienten gemessen, die sich einer Hysterolaparotomie unterzogen. Zwölf Patienten bekamen eine Allgemeinnarkose (Halothan) und systemische Opiate für die postoperativen Schmerzen; weitere zwölf Patienten bekamen eine kontinuierliche extradurale Analgesie mit einem örtlichen Narkosemittel (Bupivacain), und die übrigen 12 Patienten bekamen eine Allgemeinnarkose (Halothan) und zusatzlich extradurales Morphium (4 mg vor dem Einschnitt und weitere 4 mg beim Zumachen). Patienten, die extradurales Morphium oder Bupivacain erhielten, blieben frei von Schmerzen. Die physiologische Kortisol- und Glukose-Reaktion auf die Chirurgie wurde durch die extradurale Analgesie mittels Bupivacain blockiert. Extradurales Morphium konnte die anfängliche Steigerung der Plasmakortisol- und Glukose-Konzentrationen während der Chirurgie nicht abändern, konnte jedoch die hyperglykämische und Kortisol-Reaktion nach der Chirurgie unterdrücken, im Vergleich zu der Allgemeinnarkosegruppe, die systemische Opiate erhielt. Kortisol- und Glukosekonzentrationen waren jedoch nach der Operation bei den Patienten grösser, die extradurales Morphium bekamen, als bei denen, die extradurales Bupivacain bekamen, was vermuten lässt, dass die Endokrin-Stoffwechsel-Reaktion auf die Chirurgie vorwiegend durch neurogene Reizungen ausser Schmerzreizen ausgelöst wird, die mit opiatrezeptorabhängigen schmerzvermittelnden Bahnen verbunden sind.

INFLUENCIA DE LA MORFINA EXTRADURAL EN LA RESPUESTA ADRENOCORTICAL E HIPERGLICEMICA A LA INTERVENCION QUIRURJICA

SUMARIO

Se midieron de forma repetida las concentraciones de glucosa y de cortisol en el plasma desde antes de la inducción de la anestesia hasta 9 horas después de efectuar la incisión en la piel de 36 pacientes sometidos a histerectomía abdominal. Doce pacientes recibieron anestesia general (halotano) y opiatos sistémicos para el dolor posterior a la operación; a otros doce pacientes se les sometió a una analgesia extradural continua mediante un agente anestésico local (bupivacaína) y a los doce pacientes restantes se les sometió a anestesia general (halotano) más morfina extradural (4 mg antes de la incisión en la piel y otros 4 mg al cierre de dicha incisión). Los pacientes que recibieron morfina extradural o bupivacaína no sufrieron dolor alguno. Las respuestas fisiológicas del cortisol y de la glucosa a la intervención quirúrjica quedaron bloqueadas por la analgesia extradural efectuada con bupivacaína. La morfina extradural no modificó el incremento inicial de las concentraciones de glucosa y de cortisol en el plasma durante la intervención quirúrjica, pero suprimió la respuesta hiperglicémica y de cortisol a raíz de la operación, cuando se comparó con el grupo de anestesia general que recibió opiatos sitémicos. No obstante, las concentraciones de glucosa y de cortisol fueron mayores después de la operación, en aquellos pacientes que recibieron morfina extradural en comparación con los que recibieron bupivacaína extradural, lo que sugiere que la respuesta endócrino metabólica a la operación quirúrjica queda predominantemente liberada por el estímulo neurogénico que no sea el estímulo del dolor que conlleve rutas nociceptivas dependientes y receptoras de opiatos.

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SUPPRESSION OF ANTIDIURETIC HORMONE HYPERSECRETION DURING SURGERY BY EXTRADURAL ANAESTHESIA

F. BONNET, A. HARARI, M. THIBONNIER AND P. VIARS

SUMMARY

The concentrations of antidiuretic hormone in plasma and urine were determined in three groups of patients submitted to the same operative procedure. Seven (group I) underwent general anaesthesia with thiopentone, fentanyl and nitrous oxide and received an infusion of isotonic saline solution at 5 ml min^{-1}. Seven patients (group II) anaesthetized similarly, received isotonic saline solution 15 ml min^{-1}. In group III (five patients) anaesthesia was produced by extradural blockade. Surgery under general anaesthesia induced a significant increase in plasma and urine ADH concentrations which were not modified by the fluid load. Extradural anaesthesia suppressed almost completely the release of ADH during surgery. This effect of extradural anaesthesia could be related to the interruption of conduction along nociceptive neural pathways.

An increase in the secretion of antidiuretic hormone (ADH) in relation to surgery was suggested by Le Quesne and Lewis (1953) and Dudley, Boling and Le Quesne (1954), and subsequently confirmed by bioassay (Moran et al., 1964). More recent studies using a specific radioimmunoassay confirmed these findings (Philbin et al., 1976; Haas and Glick, 1978). The marked increase in plasma ADH concentration occurs primarily during surgery and in the period following operation (Moran et al., 1964; Moran and Zimmermann, 1967). Anaesthesia *per se* does not increase the concentration significantly (Moran et al., 1964). Although several mechanisms could induce the release of ADH during surgery two appear most likely: hypovolaemia from blood loss (Ishihara, Ishida and Oyama, 1978) and painful stimuli from the operative field (Ukaï, Moran and Zimmermann, 1968).

In an attempt to delineate the mechanisms, a randomized study was undertaken to compare the plasma and urine ADH concentrations in patients undergoing the same surgical procedure under either general anaesthesia with or without fluid loading, or extradural anaesthesia.

PATIENTS AND METHODS

Nineteen patients undergoing total hip replacement were studied. Informed consent was obtained from each patient. Patients with a documented history of renal, hepatic or cardiac failure were excluded from the study. During the 10 days preceding the operation, each patient received a diet comprising water *ad libitum*, sodium 100 mmole and potassium 60 mmole daily.

Patients were allocated randomly to three groups. In group I (control group), surgery was performed under general anaesthesia. In group II, general anaesthesia was administered as in group I with, in addition, an isotonic fluid load. In group III, extradural blockade was performed.

Each study comprised four periods: first, a 2-h control period before induction of anaesthesia; second, 1 h following the induction of general or extradural anaesthesia; the operative period and a 4-h stay in the recovery room were the third and fourth periods respectively.

Premedication (atropine 0.5 mg and diazepam 10 mg) was administered i.m. 1 h before the arrival in the operating theatre.

Group I comprised four women and three men whose mean age was 60 ± 5.5 yr. General anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen. Fentanyl 4 µg kg^{-1} was administered before the skin incision. The trachea was intubated with the aid of suxamethonium 1 mg kg^{-1} and the lungs were ventilated artificially throughout the operative procedure with a tidal volume of 12 ml kg^{-1} and a frequency of 15 b.p.m. Non-depolarizing neuromuscular blocking drugs were not administered. The trachea was extubated at the end of the operation. A solution of isotonic

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saline was infused at 5 ml min^{-1} 15 min before the induction of anaesthesia until the end of the operation. The rate of infusion was 3 ml min^{-1} for the 24 h following surgery.

Group II comprised five women and two men; mean age 56 ± 3 yr. They received the same anaesthetic as the patients in group I with in addition, a fluid load. An isotonic saline solution was infused continuously at 15 ml min^{-1} from 15 min before the induction of anaesthesia until the end of the operation. After operation the rate of infusion was 3 ml min^{-1}.

In *group III* (four women and one man, mean age 60 ± 8 yr) extradural anaesthesia was produced with 0.5% bupivacaine; after 15 min anaesthesia extended from S5 to T4 in all patients. A further injection of bupivacaine was given 2 h later through the extradural catheter. In this group, the rate of infusion of isotonic saline was as in group I.

In all the three groups, blood loss was measured carefully (swabs weighed, suction volume measured) and replaced promptly during surgery.

In all patients plasma and urine osmolalities were measured by freezing point depression (Fiske-Osmometer) and sodium and creatinine concentrations determined using a Technicon Autoanalyser. Systemic arterial pressure was recorded using an electromanometer.

The concentration of ADH was measured in urine samples collected during a control period of 2 h during anaesthesia, during surgery (mean duration: group I 187 ± 34 min, group II 125 ± 17 min, group III 172 ± 44 min) and for the first 4 h after operation. These urine samples gave a profile of ADH secretion during the whole anaesthetic period, the entire surgical procedure and the period immediately after operation. Plasma ADH concentration was measured in blood samples collected on dry heparin in glass tubes previously chilled in ice. The first blood sample was collected on arrival in the operating theatre. Three subsequent collections were made 5, 10 and 15 min after the induction of general anaesthesia or the onset of extradural anaesthesia, and were pooled. Three other samples were obtained 5, 10 and 15 min after the skin incision in each of the three groups of patients and were pooled also. A final sample was collected in the 4th hour following operation. Thus, plasma ADH concentrations were known after the induction of anaesthesia and within the first minutes of surgery and at the end of the study. Since the increase in ADH secretion could be intermittent (Weitzman et al., 1977a) the effect of anaesthesia and surgical stimulation were studied more effectively by pooling the plasma samples. Samples were immediately centrifuged at 4 °C, at 4000 rev min^{-1} for 10 min, and the plasma stored frozen at −20 °C in 2-ml aliquots acidified to pH 4.5 with hydrogen chloride 1 mol litre^{-1}. ADH concentration was determined using a previously described radioimmunoassay in urine (Fressinaud, Corvol and Menard, 1974) and plasma (Thibonnier et al., 1981).

Statistical calculations used non-parametric methods: the Kruskall–Wallis test and the Spearman rank correlation.

RESULTS

Plasma and urine ADH concentrations

Control period. Plasma ADH concentrations were within the normal range in all patients and were similar to those measured in eight healthy men after overnight fasting (1.57 ± 0.17 pg ml^{-1}) (Thibonnier et al., 1981). There were no significant differences between the three groups (table I). In all groups the ADH concentrations in urine were also in the normal range when compared with the values in 15 healthy subjects after overnight fasting (urine creatinine 53 ± 22 pg mg^{-1}) (Alhenc-Gelas et al., 1974).

Group I (figs 1, 2, table I). General anaesthesia produced insignificant increases in plasma and urine ADH concentrations. The immediate response to surgery was a dramatic and significant

TABLE I. *ADH concentrations in plasma and urine.* *$P < 0.05$; **$P < 0.01$

	Group	Plasma (pg ml^{-1})	Urine creatinine (pg mg^{-1})
Control	I	1.29 ± 0.43	65 ± 15
	II	0.98 ± 0.29	48 ± 12
	III	1.21 ± 0.28	32 ± 15
Anaesthesia	I	4.10 ± 2.84	239 ± 25
	II	0.83 ± 0.14	144 ± 97
	III	0.95 ± 0.29	39 ± 10
Surgery	I	8.82 ± 3.03*	1286 ± 513**
	II	12.21 ± 7.08*	1408 ± 671**
	III	3.10 ± 2.72	554 ± 288**
After operation	I	14.12 ± 6.81**	835 ± 390**
	II	22.36 ± 7.90**	1674 ± 801**
	III	19.56 ± 8.36**	340 ± 288**

increase in plasma ADH values substantiated by an increase in the amount of ADH excreted during the whole operation. A further increase in plasma and urine ADH concentrations occurred after operation.

Group II (figs 1, 3, table I). There were no changes in plasma and urine ADH concentrations with the induction of anaesthesia but a marked increase occurred, as in group I, following the skin incision. After operation ADH concentrations increased and were identical to those of group I in both plasma and urine.

Group III (figs 1, 4, table I). Extradural anaesthesia by itself did not modify plasma and urine ADH secretion. Surgery under extradural anaesthesia was not followed by any significant change in plasma ADH. A slight increase in the urinary concentration of ADH was noticed during surgery but remained well below the values observed in the first two groups ($P<0.01$). Following surgery (effective extradural anaesthesia lasted for 1 h) the increase in ADH concentration in the urine was much less marked than in the first two groups ($P<0.01$). By the 4th hour, plasma values were identical with those in groups I and II.

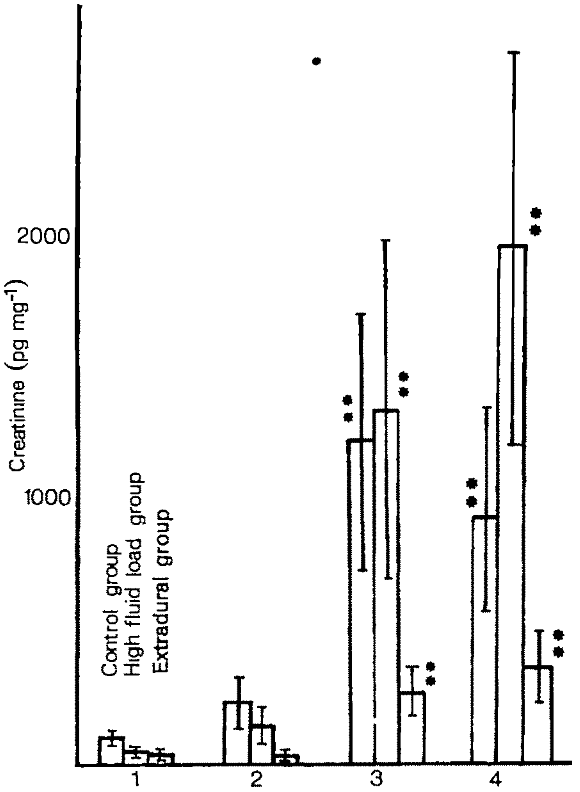

FIG. 1. Changes in ADH concentrations in urine. Values are expressed in pg mg^{-1} of creatinine because of changes in glomerular filtration during surgery. 1 = Control; 2 = anaesthesia; 3 = surgery; 4 = postoperative period. **$P<0.01$

Circulatory changes.

After the induction of general anaesthesia systolic arterial pressure decreased by 8% and 4% in groups I and II respectively. There were insignificant fluctuations during the rest of the study. Following the production of extradural anaesthesia, a decrease of 15% was observed in arterial pressure, which gradually returned to its initial value.

When the third sample for plasma ADH was taken at the 15th min after the skin incision blood losses were 160 ± 30 ml in group I, 140 ± 20 ml in group II and 145 ± 25 ml in group III. During the whole procedure blood loss was comparable in the three groups: group I 1850 ± 600 ml, group II 1700 ± 450 ml, group III 1600 ± 450 ml. Fluid retention throughout the study, estimated by the difference between the volume of saline infused

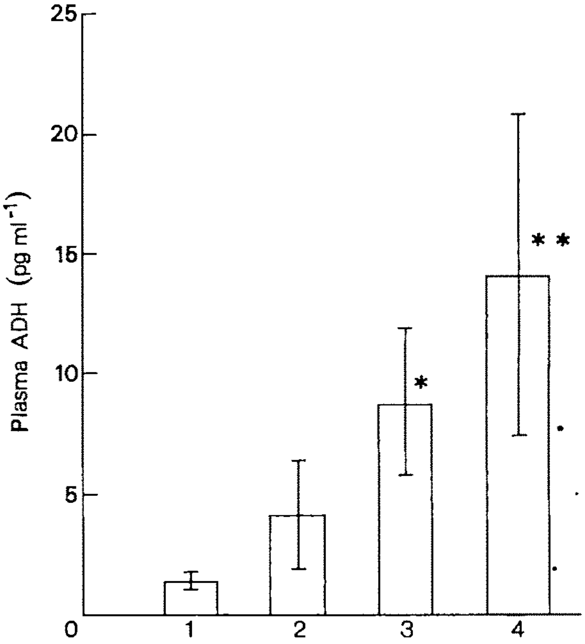

FIG. 2. Group I: changes in ADH concentrations in plasma under general anaesthesia. 1 = Control; 2 = induction of anaesthesia; 3 = skin incision; 4 = 4th hour after operation.

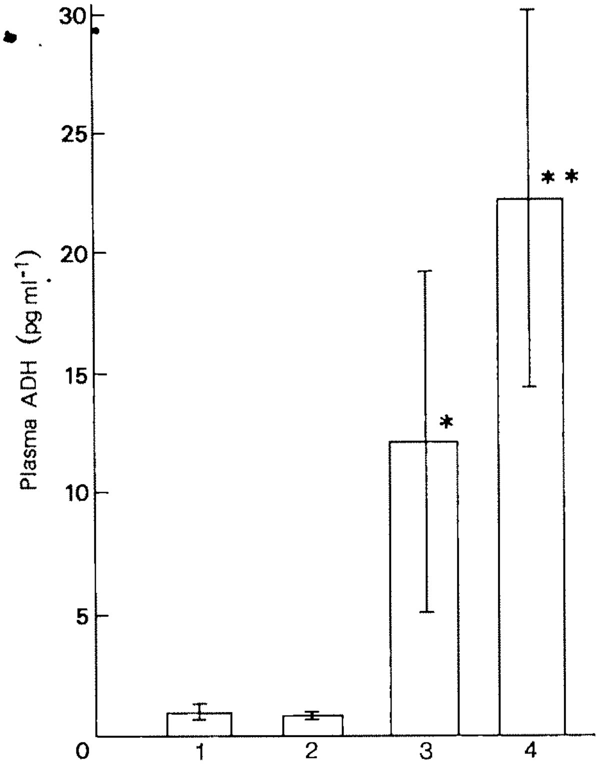

FIG. 3. Group II: effect of fluid load on plasma ADH concentrations during general anaesthesia. Periods as in figure 2.

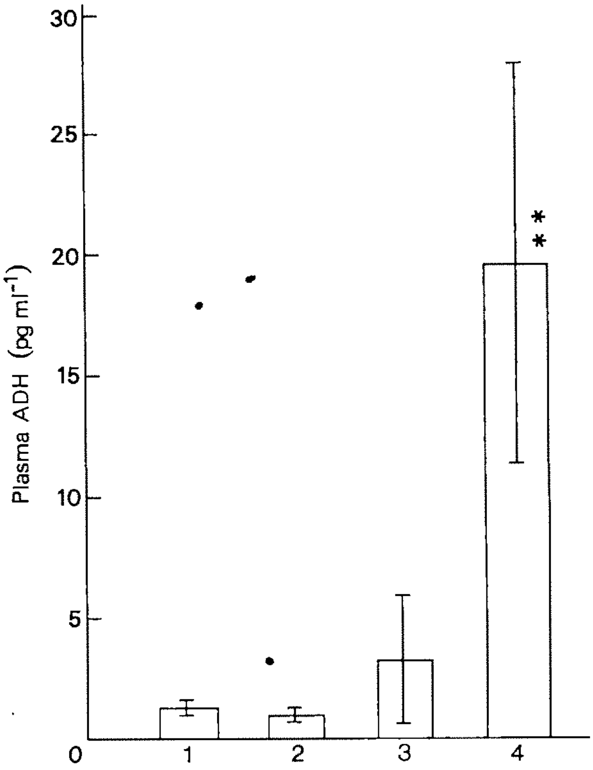

FIG. 4. Group III: changes in plasma ADH concentrations under extradural anaesthesia. Periods of study as in figure 2.

TABLE II. *Changes in plasma and urinary indices.* *$P<0.05$; **$P<0.01$

	Group	Control	Anaesthesia	Surgery	After operation
Plasma osmolality (mosmol kg^{-1})	I	288±4	289±3	289±5	293±4
	II	282±2	280±2	283±2	284±2
	III	288±2	289±2	291±3	288±3
Urine osmolality (mosmol kg^{-1})	I	699±72	683±69	637±79	681±58
	II	547±77	498±85	437±89*	580±67
	III	544±75	549±70	520±49	609±103
Urine output (ml min^{-1})	I	1.0±0.1	0.9±0.1	1.3±0.5	0.6±0.1*
	II	2.2±0.4	2.6±0.6	2.4±0.8	1.0±0.3*
	III	2.0±0.5	1.6±0.4	1.3±0.5	1.1±0.3*
Creatinine clearance (ml min^{-1})	I	121±27	125±21	74±11**	68±13**
	II	122±16	125±31	76±13**	67±17**
	III	117±7	84±15**	68±17**	50±9**
Osmolar clearance (ml min^{-1})	I	2.3±0.4	2.9±0.7	1.9±0.6	1.3±0.3*
	II	3.9±1.6	4.1±1.3	2.9±1.1	1.6±0.3**
	III	3.1±0.8	2.2±0.6	1.1±0.2*	1.5±0.3*
Free water clearance (ml min^{-1})	I	−1.3±0.2	−1.5±0.2	−0.6±0.2	−1.0±0.3
	II	−1.8±0.4	−1.6±0.8	−0.4±0.7	−0.9±0.4
	III	−1.3±0.4	−1.1±0.5	−0.5±0.1	−0.7±0.2

and the urinary volume, was more marked in group II (1740 ± 340 ml; $P < 0.01$) than in groups I (831 ± 179 ml) or III (994 ± 299 ml).

Plasma osmolality and renal function (table II)

Plasma osmolality remained constant throughout the study in all the three groups. Urine osmolality decreased significantly in group II during the operative period coinciding with the saline load. A significant decrease in urinary output and osmolar clearance was noted in all three groups after operation. Creatinine clearance was decreased in groups I and II during surgery and in the period after operation. As expected, in group III creatinine clearance decreased immediately following induction of extradural anaesthesia without fluid loading, whereas the free water clearance was negative during all periods in the three groups.

Statistics

Plasma and urine ADH concentrations were closely related in the three groups of patients ($r = 0.61$, $P < 0.001$), but these indices were not related to plasma osmolality, plasma sodium concentration, urine osmolality or free water clearance, when considering the whole study.

DISCUSSION

Simultaneous measurements of the concentration of ADH in plasma and urine demonstrated release of this hormone during surgery conducted under general anaesthesia. A fluid load did not prevent this hypersecretion, whereas extradural anaesthesia suppressed it almost completely.

The physiological control of ADH secretion involves alteration in plasma osmolality, arterial pressure and blood volume. In our study plasma osmolality remained constant throughout the operative and the postoperative periods. The ADH concentrations achieved during these periods were markedly greater than those observed after a strong stimulation of hypothalamic osmoreceptors (Moran and Zimmermann, 1967). Thus, alterations in plasma osmolality are not likely to be the factor promoting ADH hypersecretion. The lack of correlation between ADH and plasma osmolality, usually observed in normal subjects (Robertson, 1977) reinforces this assertion.

In the first two groups variations in arterial pressure were less than 10% from control. Since a relationship is documented between the changes in arterial pressure and the release of ADH (Robertson, 1977), this small decrease in systolic arterial pressure could account for the slight increase in ADH values observed after the induction of anaesthesia. However, in the group submitted to extradural anaesthesia, despite a larger decrease in arterial pressure the concentrations of ADH remained constant in plasma and urine. Only a decrease in blood volume greater than 10% can stimulate ADH release (Robertson, 1977). In our study, any influence of such volume regulation can be excluded because of careful replacement of blood loss and the infusion of saline making a significant decrease in blood volume improbable. Moreover, the increase in plasma ADH concentration was observed within a few minutes of the start of surgery before any significant blood loss had occurred. In group III when blood loss and fluid retention were identical to those observed in the control group, secretion of ADH was less. Furthermore, the fluid load in group II was unable to prevent the ADH hypersecretion induced by surgery but led to fluid retention as previously observed (Sinnatamby et al., 1974). Such an infusion has been demonstrated to be sufficient to decrease the release of ADH in normal subjects and in subjects in whom fluids have been restricted (Moore, 1971). In a recent study Ishihara, Ishida and Oyama (1978) also failed to block ADH hypersecretion after operation using a 15-ml min^{-1} infusion in dogs. Only an infusion of fluid of about 50 ml min^{-1}—10 times greater than in our control group, was able to prevent the release of ADH (Ishihara, Ishida and Oyama, 1978). Such a fluid load overcomes the compensation of hypovolaemia. The need to infuse such large amounts to counteract ADH hypersecretion induced by surgery, suggests that other factors are more important.

The release of ADH may be influenced by factors other than the physiological, such as factors related directly to anaesthesia and the surgical procedure. In this study it appeared that thiopentone and suxamethonium did not have a major influence on ADH release and therefore, are similar to previous reports about thiopentone (Ishihara, Ishida and Oyama, 1978; Leedy, Forsling and Forsling, 1979), ether (Ishihara, Ishida and Oyama, 1978; Leedy, Fossling and Fossling, 1979) and halothane (Oyama, Sato and Kimura, 1971; Forsling and Ullmann, 1975; Simpson and Forsling, 1976; Ishihara, Ishida and Oyama, 1978; Leedy, Forsling and Forsling, 1979). It has been suggested that morphine and beta-endorphin could stimulate the secretion of ADH (De Bodo, 1944; Schnieden and Blackmore, 1955; Weitzman et al., 1977b). However, the influence of morphine on the release of ADH during balanced anaesthesia is similar to that of other anaesthetic drugs (Philbin et al., 1976; Ishihara, Ishida and Oyama, 1978).

Mechanical ventilation could influence the secretion of ADH (Hemmer et al., 1980), but it has been demonstrated that intermittent positive pressure ventilation has no significant effect on the release of ADH (Philbin, Baratz and Patterson, 1970; Hemmer et al., 1980). We could observe no significant difference in ADH concentrations in plasma and urine during the anaesthetic period before surgery when comparing the first two groups submitted to arterial ventilation and extradural group of patients breathing spontaneously.

The most important finding of the present study is that extradural anaesthesia almost completely suppressed the increase in ADH concentration induced by surgery. No changes in plasma and urine concentrations were observed after extradural anaesthesia had been performed, suggesting that this anaesthetic procedure itself does not decrease or affect the release of ADH. Extradural anaesthesia achieves a non-specific blockade of sensory pathways including nociceptive pathways. That pain is able to induce an increase in plasma ADH concentration was demonstrated by cutaneous electrical stimulation in dogs (Moran and Zimmermann, 1967), a response which was suppressed by denervation of the limb in the same study. The effect of visceral pain induced by experimental gastrectomy in dogs was also blocked by anatomical interruption of nociceptive pathways by the means of either ventrolateral cordotomy or posterior rhizotomy (Ukaï, Moran and Zimmermann, 1968). In contrast, section of the vagus which contains only a few nociceptive fibres did not modify the release of ADH during the same operation (Ukaï, Moran and Zimmermann, 1968). It has been shown in one patient that, when visceral traction was applied affecting innervation above the level of extradural anaesthesia, the suppression by extradural anaesthesia disappeared (Moran et al., 1964). The importance of nociceptive stimuli is supported by the depressant effect of very high doses of morphine or fentanyl on surgically-induced release of ADH (Philbin and Coggins, 1978; Stanley, Philbin and Coggins, 1979). Furthermore, plasma and urine concentrations reached their greatest values when opiate or extradural analgesia had decreased during the early postoperative period, at which point pain was the main factor stimulating further ADH hypersecretion.

Hypersecretion of other hormones, induced by surgery, can be blocked by extradural anaesthesia (Kehlet, 1979): growth hormone (Brandt et al., 1976), cortisol (Engquist et al., 1975) renin, aldosterone (Brandt, Ølgaard, and Kehlet, 1979) and catecholamines (Roizen and Horrigan, 1979). Since surgically-induced release of hormones may be implicated in immune depression and metabolic disturbances after operation (Kehlet et al., 1979; Rem, Brandt and Kehlet, 1980) this inhibition of the endocrine response to surgery could be beneficial, but that fact is yet to be proven for ADH.

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SUPPRESSION DE L'HYPERSECRETION D'HORMONE ANTIDIURETIQUE PENDANT UNE INTERVENTION CHIRURGICALE GRACE A L'ANESTHESIE EXTRADURALE

RESUME

Nous avons déterminé sur trois groupes de patients devant subir la même intervention chirurgicale, le concentrations d'hormone antidiurétique dans le plasma et l'urine. Sept personnes (groupe I) ont été soumises à une anesthésie générale à l'aide de thiopentone, fentanyl et protoxyde d'azote, puis elles ont reçu une perfusion de solution physiologique à raison de $5\,ml\,mn^{-1}$. Sept patients (groupe II), anesthésiés d'une manière similaire ont reçu une solution physiologique à raison de $15\,ml\,mn^{-1}$. En ce qui concerne le groupe III (cinq patients), l'anesthésie a été provoquée par blocage extradural. L'opération effectuée sous anesthésie générale a provoqué une augmentation sensible des concentrations ADH dans le plasma et l'urine, concentrations qui n'ont pas été modifiées par la charge liquide. L'anesthésie extradurale a presque entièrement supprimé le dégagement d'ADH pendant l'intervention chirurgicale. Cet effet de l'anesthésie extradurale peut être relié à l'interruption de la transmission le long des voies d'accès nociceptives neurales.

UNTERDRÜCKUNG DER DIURESEHEMMENDEN HORMONHYPERSEKRETION WÄHREND DER CHIRURGIE MITTELS EXTRADURALER ANÄSTHESIE

ZUSAMMENFASSUNG

Die Konzentrationen des diuresehemmenden Hormons im Plasma und im Urin wurden bei drei Gruppen von Patienten bestimmt, die sich derselben Operation unterzogen. Sieben Patienten (Gruppe I) bekamen eine Allgemeinnarkose mit Thiopenton, Fentanyl und Stickoxydul in Verbindung mit einer Infusion von isotonischer Salzlösung $5\,ml\,min^{-1}$. Weitere sieben Patienten (Gruppe II) bekamen eine ähnliche Narkose und eine isotonische Salzlösung $15\,ml\,min^{-1}$. Bei der Gruppe III (5 Patienten) wurde die Anästhesie durch extradurale Blockade herbeigeführt. Die Chirurgie unter Allgemeinnarkose führte eine bedeutende Zunahme der diuresehemmenden Hormonkonzentrationen im Plasma und im Urin herbei, die durch die Flüssigkeitsbelastung nicht abgeändert

wurden. Die extradurale Anästhesie unterdrückte fast vollständig die Abgabe des diuresehemmenden Hormons während der Chirurgie. Diese Auswirkung der extraduralen Anästhesie könnte mit der Unterbrechung der Übertragung über schmerzvermittelnde Bahnen in Verbindung stehen.

SUPRESION DE LA HIPERTENSION OCASIONADA POR HORMONAS ANTIDIURETICAS MEDIANTE ANESTHESIA EXTRADURAL ADMINISTRADA DURANTE INTERVENCION QUIRURJICA

SUMARIO

Se determinaron las concentraciones de hormona antidiurética, en el plasma y en la orina, en tres grupos de pacientes sometidos a los mismos procedimientos operativos. Siete (grupo I) se sometieron a anestesia general con tiopentona, fentanilo y óxido nitroso y recibieron una infusión de una solución isotónica salina a un régimen de 5 ml min^{-1}. Otros siete pacientes (grupo II), anestesiados de forma similar, recibieron una solución isotónica salina a un régimen de 15 ml min^{-1}. En el grupo III (constituido por cinco pacientes) la anestesia se produjo mediante bloqueo extradural. La intervención quirúrjica bajo condiciones de anestesia general, indujo un incremento significativo en las concentraciones de hormona antidiurética en el plasma y en la urina, que no vinieron modificades por la carga de flúido. La anestesia extradural suprimió, casi completamente, la liberación de la hormona antidiurética durante la intervención quirúrjica. Este efecto de la anesthesia extradural podría estar relacionado con la interrupción de la conducción a lo largo de las rutas neurales nociceptoras.

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SINGLE-DOSE COMPARISON OF BUPRENORPHINE 0.3 AND 0.6 MG I.V. GIVEN AFTER OPERATION: CLINICAL EFFECTS AND PLASMA CONCENTRATIONS

P. J. Q. WATSON, H. J. MCQUAY, R. E. S. BULLINGHAM, M. C. ALLEN AND R. A. MOORE

SUMMARY

The plasma concentrations and clinical effects of a single i.v. dose of buprenorphine 0.3 or 0.6 mg were studied in patients recovering from surgery. Analgesic and hormonal effects were greater with the greater dose without a parallel increase in respiratory depression. A comparison with previous work suggests that increased efficacy results either from the use of the larger dose or equivalently if the first required postoperative dose of 0.3 mg has been preceded by a similar loading dose.

The pharmacokinetics of buprenorphine (Temgesic, Reckitt and Colman), a synthetic narcotic analgesic with agonist and antagonist properties, have recently been described (Bullingham et al., 1980, 1981). Results were presented for different routes of administration but only a single dose was used.

A trial was designed to study the kinetics of buprenorphine given at two different i.v. doses. Simultaneous measurements were made of the clinical effects.

This paper reports the analgesic, metabolic and respiratory effects in this trial. These are of particular interest because of the mixed agonist–antagonist properties of the drug, which may not produce straightforward dose–effect relationships (Houde and Wallenstein, 1956; Martin, Gorodetsky and Thompson, 1972).

PATIENTS AND METHODS

The study was conducted in nineteen patients undergoing elective total hip replacement for either osteo- or rheumatoid arthritis at the Nuffield Orthopaedic Centre, Oxford. Patients over the age of 80 yr and those with cardiovascular, respiratory, liver or kidney disease were excluded. Any patient taking drugs other than diuretics, oral analgesics or steroids was also excluded. All patients gave informed consent to the study which had been approved by the local Ethics Committee.

The patients were premedicated with diazepam 10 mg orally 2 h before operation. A 1.6-mm i.d. Venflon cannula was inserted i.v. under local analgesia. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained with nitrous oxide, oxygen (2 : 1) and halothane using a Bain co-axial breathing system with spontaneous ventilation through a mask and Guedel airway. The fresh gas flow was 100 ml kg^{-1}. The halothane concentration was increased initially to 2% and then reduced to 0.5% until 5 min before the end of surgery.

A lumbar extradural block was performed, with the patient in the left lateral position, at the L2–3 or L3–4 interspace. A Portex catheter was inserted and after a test dose of 0.5% bupivacaine 2 ml with 1 : 200 000 adrenaline, a further 13–17 ml of the same solution was injected with the patient supine. A 0.53-mm i.d. Longdwell was inserted into the radial artery after Allen's test had been performed, for direct arterial pressure monitoring and postoperative blood sampling.

Throughout the operation e.c.g., heart rate and arterial pressure were monitored and blood loss was assessed by swab weighing and measurement of suction loss. If the systolic arterial pressure decreased to less than 70 mm Hg, 3-mg increments of ephedrine were given. Fluid replacement was with Hartmann's solution 1000 ml followed by either blood or saline depending on blood loss and preoperative haemoglobin concentration.

After operation the patients were transferred to the recovery room where they breathed 28% oxygen through a Ventimask for at least 6 h.

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The patients were divided into two groups. Three hours after the start of surgery buprenorphine 0.3 mg (0.3-mg group) or 0.6 mg (0.6-mg group) diluted to 10 ml with normal saline was given i.v. over 30 s. Three hours later (6 h from the start of surgery) the patient was connected via a separate i.v. line (Butterfly 21-gauge) to a demand analgesia system which gave diamorphine 0.25 mg whenever the button was pressed. This system was constructed in the Nuffield Department of Anaesthetics from a modified Mill Hill infusion pump (Muirhead Ltd, 34 Croydon Road, Beckenham, Kent). It remained in place until the following morning and each demand was recorded automatically on a chart recorder. No other analgesia was given to the patient but metoclopramide 10 mg was given i.m. if the patient suffered from nausea or vomiting.

Arterial pressure, heart rate and breathing rate were recorded every 30 min initially and then hourly during the 6 h from the start of surgery. Pain intensity, degree of sedation and side-effects were recorded by the same investigator before, and at 30, 60, 120 and 180 min following the administration of buprenorphine. Pain intensity was measured on a four-point scale (0 = none, 1 = slight, 2 = moderate, 3 = severe). Sedation was assessed on a four-point scale (3 = asleep, 2 = moderately drowsy, 1 = mildly drowsy, 0 = alert).

Arterial blood-gases were analysed at 30 and 150 min after the start of surgery and at 10, 60, 120 and 180 min after the buprenorphine was given, using a Radiometer ABL2 blood-gas analysis system. Plasma glucose and plasma cortisol concentrations were measured before operation and at the same times as the arterial blood-gases. Plasma glucose was measured by a standard glucose oxidase procedure and plasma cortisol by the method of Beardwell, Burke and Cope (1968). Plasma buprenorphine samples were taken at 2, 5, 7.5, 10, 15, 20, 30, 40, 60, 80, 100, 120, 150 and 180 min after the administration of buprenorphine, and the concentrations were measured by the method of Bartlett and others (1980) using a phosphate buffer. Intra-assay and interassay variation at various plasma concentrations was less then 5%.

A continuous recording of the analgesic demands of each patient against time was obtained. This was analysed in two ways (McQuay et al., 1980). First, the time taken to the fifth demand by each patient was chosen to estimate the duration of analgesia and the median value for the patients in each group was compared. Second, to compare the requirement for further analgesia in the two groups, the number of demands made by each patient during each 15-min period from 0 to 540 min was averaged for each group. We took 540 min as it was the minimum time for which intact records were available.

These cumulative mean demands were plotted against time (fig. 1). Regression slopes were calculated and are shown drawn through the points in figure 1. The ratio between the slopes was obtained. This method of regression slope calculation was used to separate the effects of dose and sex.

RESULTS

There were no significant differences between the two groups in respect of age, sex ratio, height, time of surgery and blood loss (table I). There was a significant difference in weight, the heavier group receiving the larger dose of buprenorphine.

TABLE I. *Patient data (mean ± SEM)*

	Group	
	0.3 mg	0.6 mg
Number	9	10
Age (yr)	66.2±2.9	59.9±3.8
Weight (kg)	62.7±3.6	72.1±3.9
Height (cm)	170.0±2.4	167.3±3.0
Surgery time (min)	86.7±7.1	94.5±11.4
Blood loss (ml)	329.0±57.0	489.0±89.0
Sex ratio	5M:4F	5M:5F

Two patients from the 0.3-mg group could not be included in the analgesia demand analysis because no recordings were obtained. One patient from each group was excluded from the analysis of metabolic results because they were on steroid medication.

Operating conditions were very good and there were no complications during the anaesthetic.

After operation the patients wakened quickly, and had pain intensity scores of 0 before the buprenorphine was given. After buprenorphine all the patients remained pain free (pain intensity

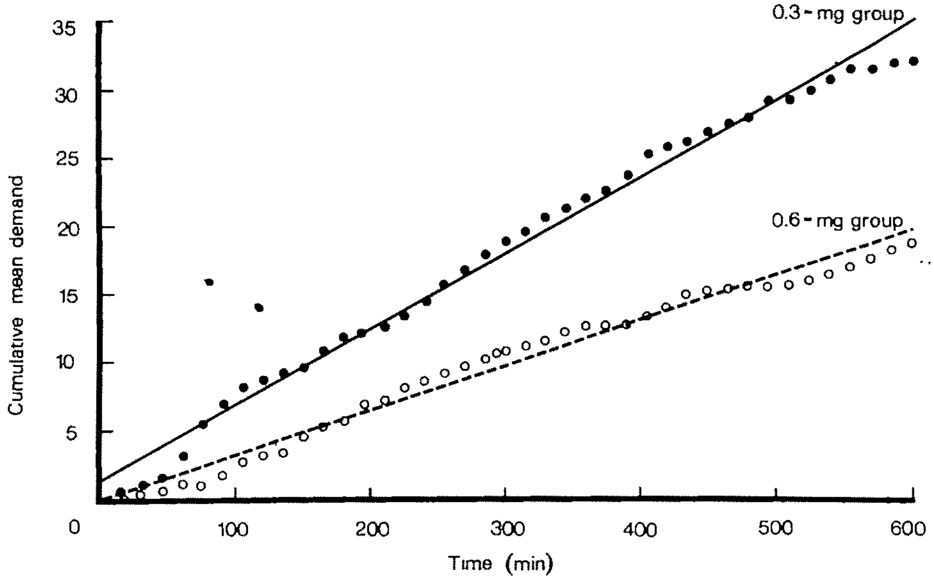

FIG. 1. Cumulative mean dose of diamorphine administered via demand system for the two groups. 0.3-mg group: $n = 7$, $r = 0.994$; 0.6-mg group: $n = 10$, $r = 0.990$.

score 0) for at least 120 min. At 180 min, two-thirds of the patients had slight pain, and one-third had no pain, there being no difference between the two groups or between the sexes.

On wakening, the patients were all alert or mildly drowsy, with sedation scores of 0 or 1, except for one patient who was moderately drowsy. After buprenorphine, all the patients were either moderately drowsy or asleep (sedation scores of 2 or 3) for at least 120 min, but were easily roused. Again there was no difference, either between groups or between sexes. The only other side-effects noted were nausea and vomiting. Three patients in the 0.3-mg group were nauseated and one patient in the 0.6-mg group had nausea and vomiting. In each case this was relieved by metoclopramide 10 mg i.m.

There was no marked change in heart rate or arterial pressure in either group during the 3 h after buprenorphine administration.

Plasma buprenorphine

The mean plasma buprenorphine concentrations for the two groups are shown in figure 2. At each sampling time the ratio of the concentrations approximated to the ratio of the doses. The mean value of the ratio between the plasma concentrations (0.6-mg group : 0.3-mg group) was not significantly different from 2. Full kinetic analysis of the data will appear elsewhere.

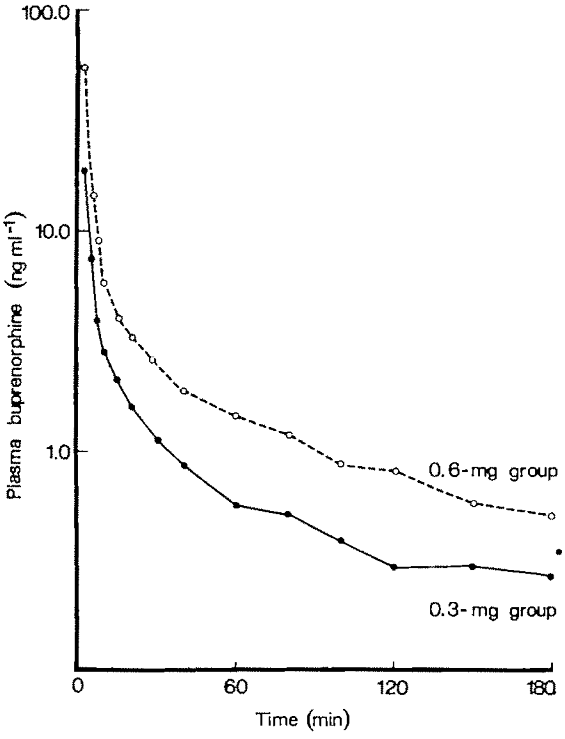

FIG. 2. Mean plasma buprenorphine concentrations on a logarithmic scale. $n = 9$ in the 0.3-mg group, $n = 10$ in the 0.6-mg group.

Glucose and cortisol

The plasma glucose and cortisol results are shown in table II. There was no significant difference between the glucose values of the two groups at any of the sampling times. Within the groups the plasma glucose continued to increase after operation after buprenorphine was given.

The 0.3-mg group had significantly greater cortisol values than the 0.6-mg group at 300 and 360 min ($P<0.05$, Student's *t* test), that is at 2 and 3 h respectively after the dose of buprenorphine was given. Within the groups, there was a significant mean increase in plasma cortisol in the 0.3-mg group at 300 min (154 nmol litre^{-1}, $P<0.1$, paired *t* test), and at 360 min (354 nmol litre^{-1}, $P<0.025$, paired *t* test). In the 0.6-mg group the increase was not significant (96 nmol litre^{-1} by 360 min).

Respiration

The arterial blood-gas results are shown in table III. There was no significant difference between the groups for Pa_{O_2}, Pa_{CO_2}, respiratory rate or $(PA_{O_2}-Pa_{O_2})$ at any of the sampling times. All of these measures showed wide ranges. The respiratory rate and Pa_{O_2} were reduced by about 30% in both groups within 10 min of giving the buprenorphine dose. Within the groups, there was a significant decrease in Pa_{CO_2} between the 300- and 360-min samples in the 0.3-mg group ($P<0.05$, paired *t* test), but not in the 0.6-mg group. $(PA_{O_2}-Pa_{O_2})$ difference was within normal limits at all times.

TABLE II. *Plasma glucose and cortisol values (mean ± SEM). Sample times calculated from the start of surgery. Buprenorphine given at 180 min.* n = *8 for 0.3-mg group,* n = *10 for 0.6-mg group*

Sample time (min)	Glucose (mmol litre^{-1})		Cortisol (nmol litre^{-1})	
	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group
0	4.50 ± 0.27	4.83 ± 0.17	303 ± 73	299 ± 40
30	5.44 ± 0.20	6.07 ± 0.40	558 ± 154	586 ± 69
150	6.75 ± 0.54	7.54 ± 0.78	862 ± 112	876 ± 98
190	6.81 ± 0.45	8.10 ± 0.81	873 ± 112	778 ± 100
240	7.39 ± 0.66	8.32 ± 0.61	923 ± 131	775 ± 126
300	7.21 ± 0.49	7.84 ± 0.35	1027 ± 131	774 ± 132
360	7.64 ± 0.78	8.39 ± 0.46	1227 ± 153	874 ± 120

TABLE III. *Blood-gas analysis results. Mean ± SEM.* n = *9 for 0.3-mg group;* n = *10 for 0.6-mg group. Sample times calculated from the start of surgery. Buprenorphine given at 180 min.* FI_{O_2} = *0.28, but 0.33 at 30-min sample time. Ranges in parentheses*

Sample time (min)	Pa_{O_2} (kPa)		Pa_{CO_2} (kPa)		Respiratory rate (b.p.m.)		$(PA_{O_2}-Pa_{O_2})$ (kPa)	
	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group
30	20.09 ± 1.5	17.29 ± 0.7	6.61 ± 0.4 (4.7–7.3)	6.38 ± 0.1 (3.7–6.4)				
150	17.51 ± 1.5	19.33 ± 1.1	5.57 ± 0.2 (4.7–7.3)	5.45 ± 0.3 (3.7–6.4)	16.7 ± 1.9	17.8 ± 1.1	2.19 ± 1.4	0.95 ± 1.1
190	12.60 ± 1.3	11.61 ± 1.9	6.60 ± 0.4 (5.0–8.6)	6.75 ± 0.3 (4.7–8.1)	12.8 ± 0.8	11.2 ± 1.0	5.94 ± 0.9	3.16 ± 0.9
240	13.41 ± 1.1	14.39 ± 0.9	6.98 ± 0.4 (5.6–9.7)	7.53 ± 0.3 (5.5–8.7)	10.8 ± 0.8	10.8 ± 1.0	4.64 ± 0.8	2.94 ± 0.8
300	13.36 ± 1.2	15.03 ± 0.9	6.80 ± 0.4 (5.6–9.8)	7.11 ± 0.4 (4.6–9.1)	11.2 ± 1.5	11.0 ± 0.8	4.16 ± 0.8	2.78 ± 0.6
360	12.43 ± 1.0	13.66 ± 0.9	5.88 ± 0.4 (4.3–8.1)	6.77 ± 0.3 (4.3–7.9)	13.0 ± 1.7	12.0 ± 0.8	5.56 ± 0.4	3.87 ± 0.7

TABLE IV. *Analgesic demand analysis by group and by sex (mean ± SEM), for 0–540 min of connection to the demand system. All the values were significantly different (P < 0.01, d.f. = 36) from all other values by comparison of the regression slopes*

	Demand rate for diamorphine ($mg \times 10^{-3}$ per patient per min)		Male/female ratio
	Males	Females	
0.3 mg i.v. ($n = 7$)	18.75 ± 0.5 ($n = 4$)	8.62 ± 0.25 ($n = 3$)	2.2
0.6 mg i.v. ($n = 10$)	13.00 ± 0.5 ($n = 5$)	4.25 ± 0.03 ($n = 5$)	3.1
0.3 mg : 0.6 mg ratio	1.4	2.0	

Analgesia

Duration of analgesia. The median time to the fifth demand for the 0.3-mg group was 250 min, compared with 492 min for the 0.6-mg group. This difference was significant ($P < 0.025$, Mann–Whitney U test).

Requirement for further analgesia. Table IV contains the regression slopes and demand ratios calculated as described. The analysis shows essentially independent effects of dose and sex. The 0.3-mg group made more demands than did the 0.6-mg group. Males made more demands than females. The influence of sex was more important than that of dose.

DISCUSSION

The relation between dose and response is fundamental to the optimal clinical use of any drug. The anticipated increase of response with increased dose does not necessarily occur with the opiates of mixed agonist-antagonist type (Martin, Gorodetsky and Thompson, 1972). These drugs can produce dose–response curves which display a maximum, minimum or the usual sigmoid-shaped response curve as the dose increases. The use of different doses of buprenorphine in this trial provided an opportunity to assess the dose–response curve for single doses in the recommended dose range.

The analgesic duration of buprenorphine 0.6 mg was twice that found with 0.3 mg. Similarly, the requirement for further analgesia after 0.6 mg was about half that after 0.3 mg. The greater dose also had greater effect than the smaller dose in preventing the anticipated increase in plasma cortisol after operation. The analgesic response to the two buprenorphine doses used, and the effect on plasma cortisol show that, in this dose range, a significant increase in response is achieved by doubling the dose.

The effect of both the doses on respiration was predictable; Pa_{CO_2} was increased and the respiratory rate decreased. There were, however, no significant differences between the groups, so that a straightforward dose–response relation was not obtained. The longer duration of the 0.6-mg dose, seen with analgesia, was also detected with respiration, because the Pa_{CO_2} values 3 h after the dose of buprenorphine had not decreased significantly from the values 1 h earlier, whereas a significant decrease was seen at this time in the 0.3-mg group.

These results show that buprenorphine produced significantly increased analgesia and hormonal response at the greater dose without an equivalent increase in respiratory depression.

The ability to differentiate the analgesic and respiratory potency of analgesics relies on the adequacy of the measurements. Most reported clinical studies of the effects of opiates involved different patient groups for the effects on respiration and analgesia. Laboratory studies either involved human volunteers who were not in pain or used animal pain models. Although refined respiratory measurements have been available, analgesic estimates have previously been relatively crude.

In this study the analgesic, respiratory and hormonal effects were measured simultaneously in patients recovering from surgery. The technique of demand analgesia used here has proved to be a sensitive method with small patient numbers as shown by the excellent linear correlation seen in figure 1. The use of Pa_{CO_2} as a respiratory measure is justified because it is still the primary physiological parameter which should determine clinical intervention. In addition, opiate drugs may cause measurable changes in hormone concentrations to occur (Moore, McQuay and Bullingham, 1980), and these changes may be used to analyse dose–response relationships. Biochemical assays may be performed with convenience and precision on stored blood samples, in contrast to analgesic and respiratory measurements.

There is both clinical and experimental support for differentiating the dose–response curves for analgesia and respiratory depression. Clinically, large doses of buprenorphine (up to 8 mg) have been used to provide analgesia without evidence of serious respiratory sequelae (K. Budd, personal communication), and the repeated use of 0.3-mg doses of buprenorphine produced increased analgesia without parallel increase in respiratory depression (McQuay et al., 1980). Experimentally, Pasternak, Childers and Snyder (1980) and Pasternak, Zhang and Tecott (1980) distinguished opiate receptor populations in mice; those receptors with high affinity binding for morphine were correlated with analgesia, and those with low affinity binding with respiratory effects. This experimental dissociation between analgesia and respiratory depression indicates a potential mechanism for the distinction seen clinically in this trial.

The analgesic effect of two 0.3-mg doses given 3 h apart (McQuay et al., 1980) may be compared with those from a single 0.3- and 0.6-mg dose in this trial. The comparison shows that the requirement for further analgesia is different; a preliminary 0.3-mg i.v. dose lowers the subsequent analgesic requirement by a factor of two from 13 to 7 µg of diamorphine per patient per min, compared with a single 0.3-mg dose after operation. The effect of a single 0.6-mg dose (diamorphine 8.5 µg per patient per min) closely resembles that of the same dose split in two and separated by 3 h. For most drugs, splitting a dose into two equal parts would be expected to produce a substantial increase in clinical effect (Wagner, 1968). The increase seen in the comparison above is small, and is a result of two factors.

First, buprenorphine is lipophilic, and hence undergoes rapid tissue uptake. Low plasma concentrations are achieved quickly (fig. 2). The liver will eliminate most of the drug passing through it (Bullingham et al., 1980), but the absolute amount destroyed is small relative to the total quantity in the body. These extensive body stores maintain the plasma concentration over a long time period. The addition of a second dose, behaving independently, at a time interval small in comparison with the time scale of the plasma concentration decay, is little different from giving the two doses simultaneously. The plasma concentration 3 h after a single 0.6-mg dose of buprenorphine was given was no different from the concentration 3 h after a second 0.3-mg dose (Bullingham et al., 1980).

Second, buprenorphine is pharmacologically effective at low plasma concentrations. This is shown by the sublingual use of the drug, which works well at plasma concentrations of 1 ng ml^{-1} or less (Bullingham et al., 1981). It is this which is the unique feature of buprenorphine. Other lipophilic drugs such as fentanyl behave in an equivalent way with regard to kinetics (McQuay et al., 1979), but depend on high initial plasma concentrations for their analgesic action.

In summary, these results show that better analgesia may be obtained with buprenorphine as a postoperative analgesic either as the larger dose or by splitting this dose. This choice can be made with buprenorphine but not pure agonists because, with the latter, any increase in analgesia will necessarily incur further respiratory depression. Where an opiate premedication is desired, it would be both logical and convenient to choose the divided dose regimen, with the first dose as premedicant.

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COMPARAISON D'UNE DOSE UNIQUE DE BUPRENORPHINE DE 0,3 ET DE 0,6 mg I.V. ADMINISTREE APRES L'OPERATION: EFFETS CLINIQUES ET CONCENTRATIONS DANS LE PLASMA

RESUME

Des études ont été réalisées en ce qui concerne les concentrations dans le plasma et les effets cliniques d'une dose unique de buprénorphine de 0,3 ou de 0,6 mg i.v. administrée à des patients en récuperation d'opérations. Les effets analgésiques et hormonaux ont été plus prononcés avec la dose plus élevée sans qu'il y ait une augmentation parallèle de la dépression respiratoire. Une comparaison avec des expériences préalables indique que l'efficacité accrue découle soit de l'utilisation d'une dose plus forte ou, de même, lorsque la première dose postopératoire requise de 0,3 mg était précédée d'une dose de charge analogue.

DOSISVERGLEICH ZWISCHEN 0,3 UND 0,6 mg BUPRENORPHIN, INTRAVENÖS NACH DER OPERATION VERABREICHT: KLINISCHE WIRKUNGEN UND PLASMAKONZENTRATIONEN

ZUSAMMENFASSUNG

Plasmakonzentrationen und klinische Wirkungen einzelner intravenöser Injektionen von 0,3 oder 0,6 mg Buprenorphin wurden bei Patienten studiert, die sich von einer Operation erholten. Analgetische und hormonale Wirkungen waren bei der grösseren Dosis stärker—ohne gleichzeitigen Anstieg der respiratorischen Dämpfung. Ein Vergleich mit früheren Arbeiten zeigt, dass die erhöhte Wirksamkeit entweder ein Ergebnis der höheren Dosis ist, oder davon, dass die erste postoperative Dosis von 0,3 mg nach einer gleichgrossen einleitenden Dosis erfolgte.

COMPARACION DE DOSIS UNICA DE 0,3 Y DE 0,6 mg DE BUPRENORFINA I.V. DESPUES DE LA OPERACION: EFECTOS CLINICOS Y CONCENTRACIONES EN EL PLASMA

SUMARIO

Se llevó a cabo el estudio de las concentraciones en el plasma y de los efectos clínicos de una dósis única i.v. de 0,3 ó de 0,6 mg de buprenorfina en pacientes bajo recuperación de una operación. Los efectos analgésicos y hormonales fueron mayores con las dosis mayores sin aumento paralelo en la depresión respiratoria. Una comparación con trabajos previos hace pensar que la eficacia mayor resulta ya sea del uso de una dosis mayor ya sea cuando la primera dosis postoperatoria necesaria de 0,3 mg fue precedida por una dosis de carga análoga.

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ELECTROENCEPHALOGRAPHIC EFFECTS OF SUFENTANIL ANAESTHESIA IN MAN

J. G. BOVILL, P. S. SEBEL, A. WAUQUIER AND P. ROG

SUMMARY

The effects of anaesthesia with sufentanil 15 µg kg^{-1}, air and oxygen on the electroencephalograph were studied in 12 patients before and after cardiopulmonary bypass. The e.e.g. responses were characterized by high voltage, slow delta waves. Although the mean power in the delta band declined with time, the contribution of delta power to total power in the frequency range 0.5–40 Hz remained constant until the onset of cardiopulmonary bypass. Sharp waves of uncertain neurophysiological significance were seen. They were not associated with clinical signs of epileptic activity. The use of the e.e.g. response as a monitor of "depth of anaesthesia" during high-dose opioid anaesthesia may become possible.

The use of large doses of opioid analgesics as anaesthetic agents for cardiac surgery was proposed by Lowenstein and colleagues (1969) who used morphine 0.5–3.0 mg kg^{-1} as the anaesthetic. More recently, anaesthesia with fentanyl 50–100 µg kg^{-1} has been advocated (Stanley and Webster, 1978; Lunn et al., 1979) since, in addition to providing a high degree of cardiovascular stability, fentanyl anaesthesia decreases the hormonal responses to surgery, although those to cardiopulmonary bypass are unaffected (Stanley et al., 1980; Sebel et al., 1981a).

Sufentanil is a synthetic opioid analgesic. It is extremely potent, being 4520 times as potent as morphine in the tail withdrawal test in rats and is also safe, the LD_{50}/ED_{50} ratio in rats being 25 211 (morphine = 67, fentanyl = 277). Dogs given sufentanil 5 mg kg^{-1} have survived and recovered after 96 h (Niemegeers et al., 1976).

Clinical experience in man suggests that sufentanil is five to 10 times as potent as fentanyl and produces minimal cardiovascular depression (de Castro, 1976; Van de Walle, Lauwers and Andriaensen, 1976; Rolly, Kay and Cockx, 1979). Reddy and colleagues (1980) demonstrated that infusions of sufentanil up to 40 µg kg^{-1} min^{-1} produced little change in cardiovascular dynamics in dogs treated with atropine and have suggested that the drug be evaluated as an anaesthetic in man.

As a part of this evaluation, we have studied the effects of anaesthesia with sufentanil 15 µg kg^{-1} on the electroencephalogram in patients undergoing cardiac surgery.

PATIENTS AND METHODS

Twelve patients undergoing coronary artery bypass (nine patients) or valve replacement (three patients) surgery were studied. The mean age was 57±2.1 yr and the mean weight 74±2.7 kg. Informed consent was obtained at the pre-operative visit.

The patients were premedicated with lorazepam 4–5 mg by mouth 1.5 h before surgery. A radial artery cannula, a central venous catheter and two wide-bore peripheral cannulae were inserted percutaneously under local analgesia before the induction of anaesthesia and e.c.g. electrodes were applied. Silver chloride "stick-on" electrodes were fixed to the scalp with 8% collodium to permit e.e.g. recording. Records were obtained on an eight-channel Beckman Accutrace recorder with the amplifiers set at 50 µV cm^{-1}, filters at 50 Hz and time constant at 0.3 s. The leads used were:

(1) Left fronto-polar→left mid-temporal (F_{p1}–T_3)
(2) Left mid-temporal→left occipital (T_3–O_1)
(3) Right fronto-polar→right mid-temporal (F_{p2}–T_4)
(4) Right mid-temporal→right occipital (T_4–O_2)
(5) Left mid-temporal→vertex (T_3–C_0)
(6) Vertex→right mid-temporal (C_0–T_4)

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The e.c.g. was recorded on channel 7 and eye movement derived from an electrode placed on the infra-orbital margins was recorded on channel 8. Derivation 5, T_3–C_0 was recorded onto magnetic tape using a Tandberg Instrumentation Tape Recorder (series 100) for subsequent off-line computer analysis.

Following a control period of at least 6 min, pancuronium 2 mg was administered i.v. and anaesthesia induced with sufentanil 15 $\mu g\,kg^{-1}$ i.v. over 2 min. Pancuronium 6 mg was administered when the patient became unresponsive. The lungs were ventilated manually for 5 min, the trachea intubated and artificial ventilation was continued with an air and oxygen mixture (FI_{O_2} 0.5). A nasogastric tube was inserted and thermocouples positioned. The e.e.g. was recorded continuously until the start of cardiopulmonary bypass. E.e.g. analysis was not attempted during cardiopulmonary bypass because of the changes associated with hypothermia (26 °C) and bypass. Following bypass the e.e.g. was recorded intermittently on paper. A visual interpretation of all the paper records was made by one of the authors (P. R.). Subsequent off-line computer analysis was carried out using a PDP11/E10 computer system. Power spectral analysis, using a Fast Fourier Transformation, was carried out for each 30-s epoch and the power contained in the frequency bands, delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–13.0 Hz) and beta (13.0–25.0 Hz) calculated. Digitization at a rate of 200 s^{-1} allowed a frequency band pass band of 0–100 Hz, resolution ±0.2 Hz. Spindle power was also calculated. The power in the various bands was then plotted on an

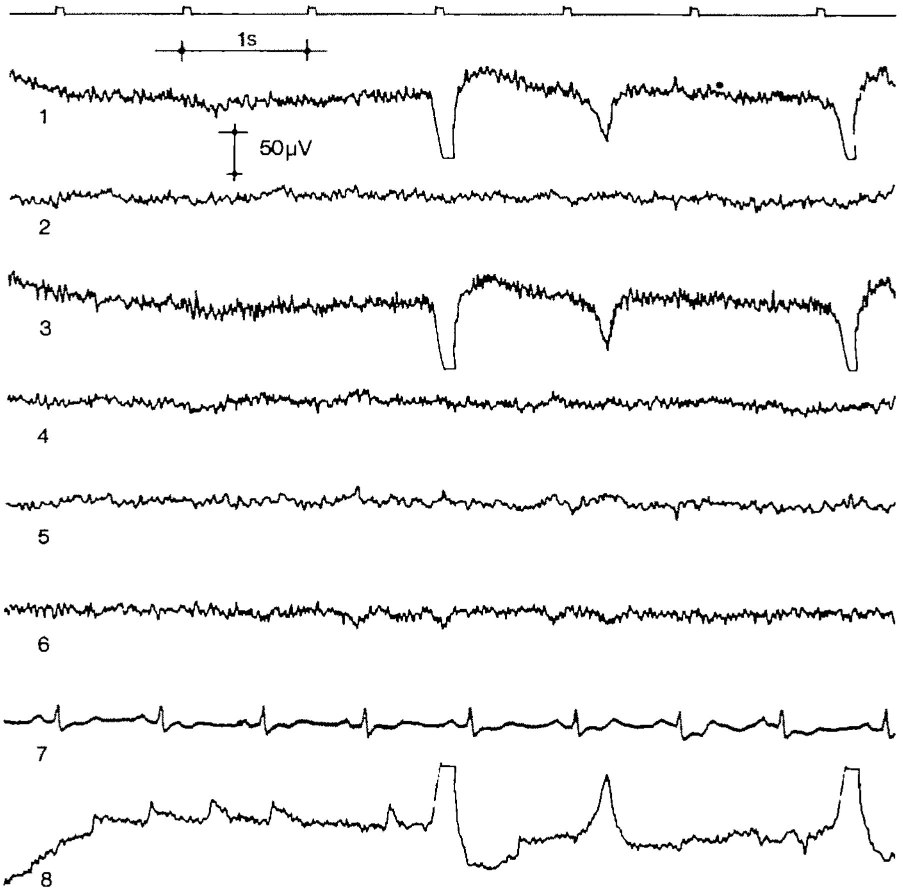

FIG. 1. Example of the e.e.g. after premedication. Leads 1–8 are as described in methods. This shows fast-wave activity with some muscle activity. The "waves" at 4.5 and 7 s are a result of eye movements.

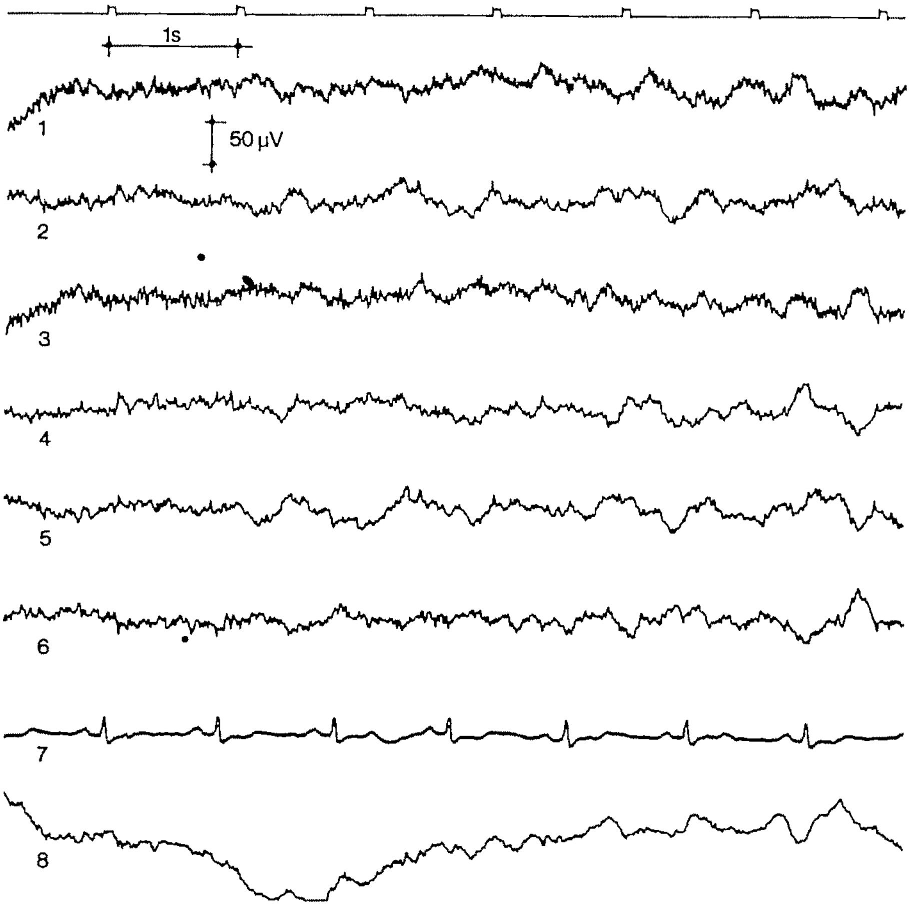

FIG. 2. Example of the e.e.g. 1 min after start of induction. Leads 1–8 are as described in methods. The overall activity is slower. Theta activity is seen and a slow eye movement is seen in lead 8.

X–Y recorder. Three-dimensional power spectral analysis was performed for the frequency range 0.5–15 Hz.

Data analysis of the e.e.g. signals for the group of 12 patients was carried out using the technique described by Wauquier and others (1979). Essentially, the mean power in each of seven predefined frequency bands from 0.5 to 40 Hz was calculated for each 6 min 15 s recording time (4 min 36 s analysis time + calculation and printing time). This was repeated for each record. Relative power was calculated as follows: for each time interval the total power (0.5–40.0 Hz) was equalized at 100% and the relative contribution to the total power contained in each of the predefined frequency bands calculated. All patients were visited by one of the authors (P. R.) 4–5 days after surgery and questioned as to awareness or memories of the procedure.

RESULTS

The appearance of the e.e.g. following the administration of sufentanil was similar in all patients. Typical examples of the changes observed are shown in figures 1–3. Within 30–60 s from the start of induction, the alpha rhythm became slower and broader and slow eye movements were seen. This was followed rapidly by diffuse theta activity and some delta waves. Delta activity increased, and by 3 min after the start of induction, there was continuous high voltage slow (0.5–2 Hz) delta wave activity which became synchronized in 50% of the patients. During the following 10–15 min, the e.e.g.

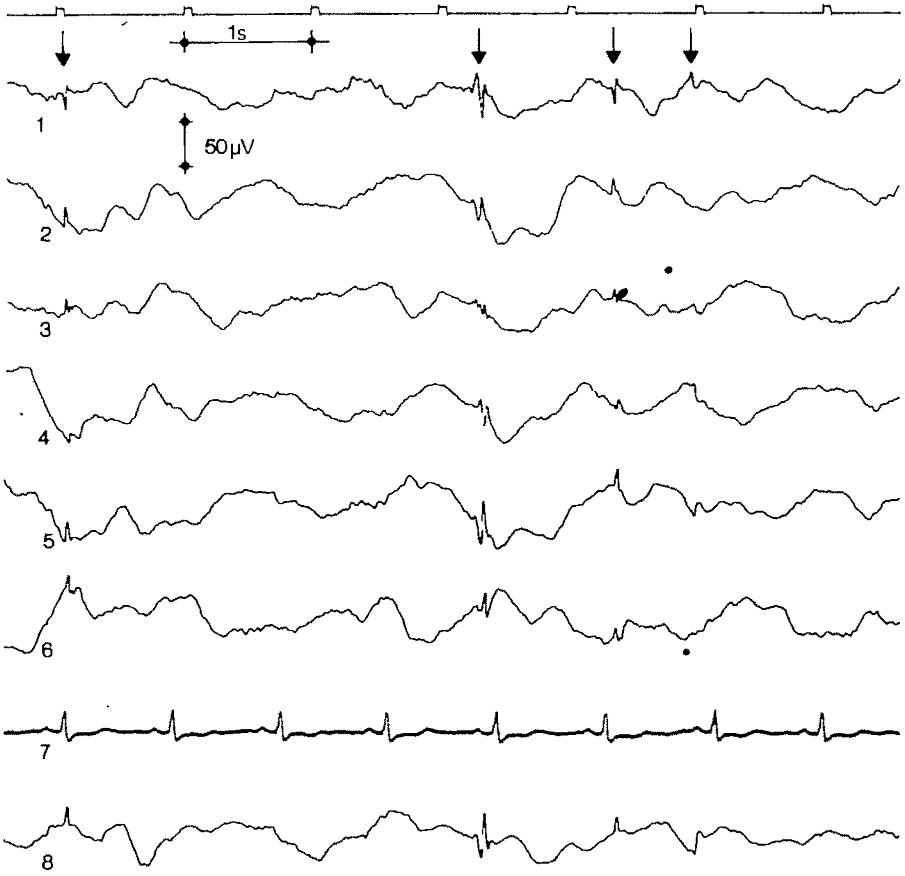

FIG. 3. Example of the e.e.g. 3 min after start of induction. Leads 1–8 are as described in methods. The main e.e.g. activity is in the delta range. "Sharp waves" are arrowed.

became more irregular with a lower voltage, and theta activity again became obvious after which the pattern remained constant until the onset of cardiopulmonary bypass. No changes in the e.e.g. were observed in any patient during tracheal intubation, skin incision or sternotomy. Following skin incision, diathermy caused considerable interference to the e.e.g. signal, although there were always sufficient uninterrupted segments available for visual analysis. After cardiopulmonary bypass, delta activity remained evident although the amplitude was less and there was an increase in theta activity. Intermittent alpha activity was observed at the end of the operation in only one patient, 5 h after induction.

Isolated sharp wave activity was observed in all patients within 2 min of induction (fig. 3). This was most obvious in the fronto-temporal region and occurred with a frequency of 8–12 min^{-1} during the initial 10–15 min and then disappeared in all but two patients, in whom they continued until the onset of cardiopulmonary bypass. They were mainly tri-phasic with a period of 30–60 ms and an amplitude of 10–70 µV. Sharp wave activity was never seen after bypass and was not associated with other signs of epileptic activity.

A representative example of three-dimensional power spectral analysis from one patient is shown in figure 4 and wide-band power spectral analysis from the same patient in figure 5. In the period before the induction of anaesthesia there was predominant beta-activity and to a lesser extent alpha-activity in all patients. Immediately following the injection of sufentanil, the power in the alpha and beta bands decreased, whereas it increased in the theta and delta bands. However within 10–15 min of induction the theta power

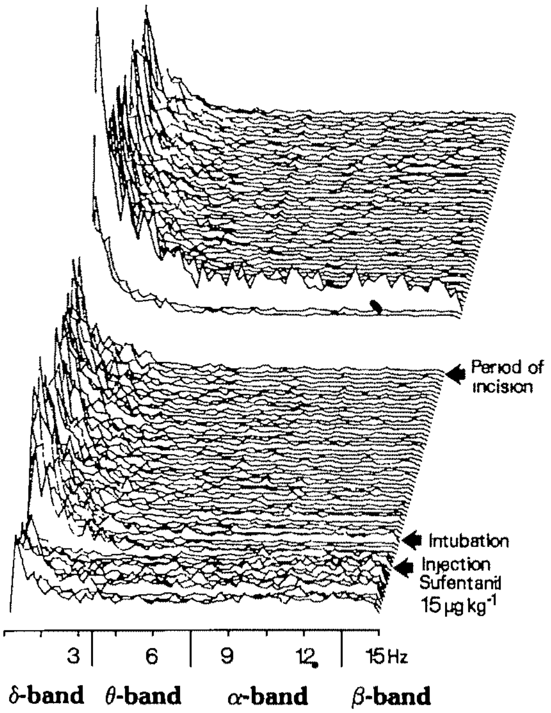

FIG. 4. Example of three-dimensional power spectral analysis of a sufentanil e.e.g. using T_3–C_0 derivation. Power is plotted vertically. Each line represents 1 min in time. The blank period after incision is because of diathermy artefact. This plot shows the change from alpha activity to delta activity that occurs on induction of anaesthesia and the constancy of the delta power.

had decreased to pre-induction values. Delta band power also decreased slightly during this period and then remained constant until the start of bypass. Neither tracheal intubation nor surgical stimuli altered the spectral pattern. During the time of the skin incision the computer was unable to analyse segments containing artefacts caused by diathermy.

The power spectral analysis for the group of 12 patients for the frequency range 0.5–40.0 Hz is shown in figure 6 and the relative power in figure 7. Total power increased following induction with sufentanil, being maximum between 12 and 18 min. This increase was predominantly because of an increase in the power in the delta (0.5–3.5 Hz) and theta (3.5–7.5 Hz) bands. The power in the theta band then decreased to pre-

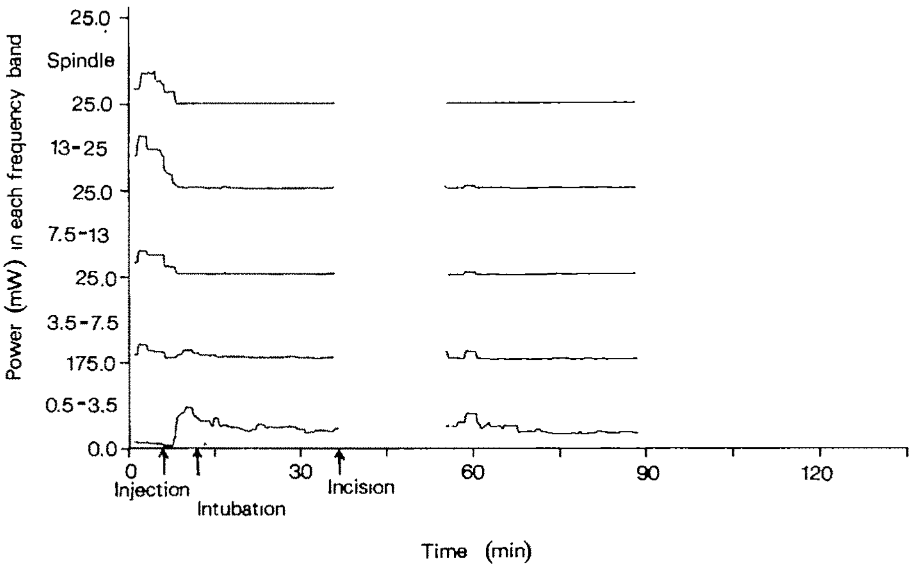

FIG. 5. Wide-band spectral analysis of the same e.e.g. as in figure 4 (T_3–C_0). Time is shown on the horizontal axis. The vertical axis shows power in mW in each frequency band (delta: 0.5–3.5 Hz; theta: 3.5–7.5 Hz; alpha: 7.5–13 Hz; beta: 13–25 Hz). The blank section is a result of diathermy artefact. This plot shows that power in the delta band is the major e.e.g. feature. Premedication: lorazepam 5 mg; anaesthesia: sufentanil.

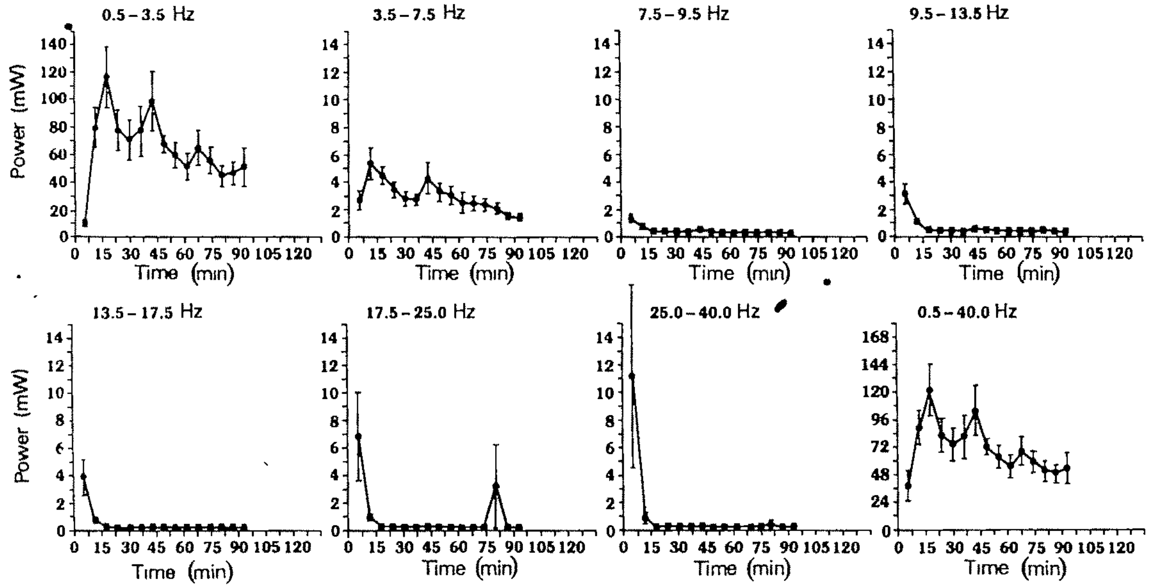

FIG. 6. Absolute e.e.g. power (mW) for 12 patients, plotted as mean ± SEM in the following bands: delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha$_1$ (7.5–9.5 Hz), alpha$_2$ (9.5–13 Hz), beta$_1$ (13.5–17.5 Hz), beta$_2$ (17.5–25 Hz), beta$_3$ (25–40 Hz) and total power in all bands. The peak in the beta$_2$ band at 80 min was caused by an artefact. The decrease in absolute delta power with time is seen.

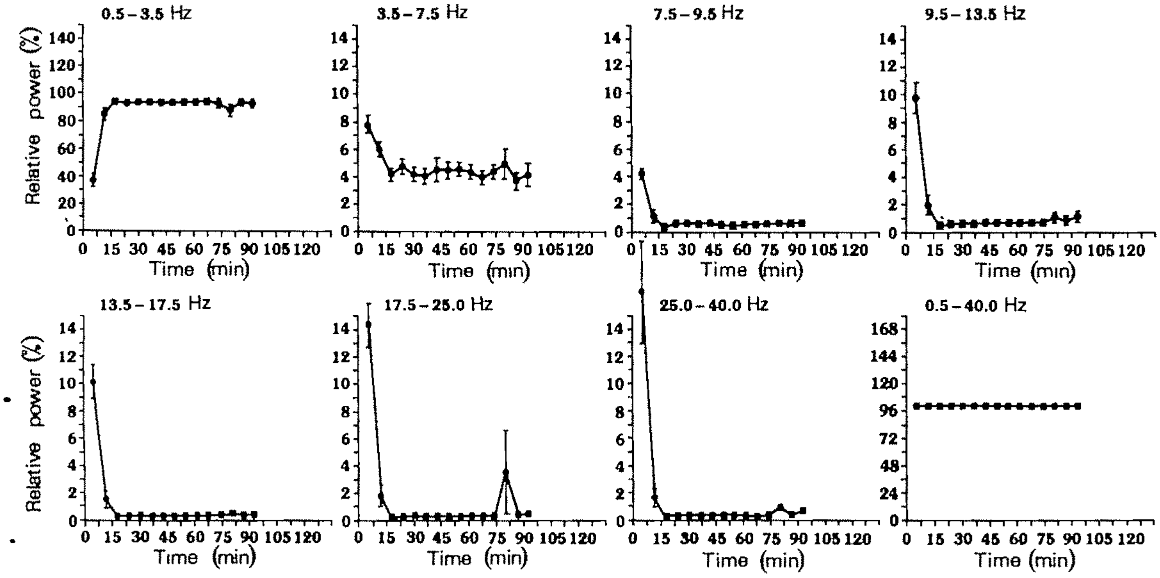

FIG. 7. Relative e.e.g. power (%) as a percentage of total power (equalized at 100%) in the following bands: delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–9.5 Hz), alpha$_2$ (9.5–13 Hz), beta (13.5–17.5 Hz), beta$_2$ (17.5–25 Hz), beta$_3$ (25–40 Hz) and total power in all bands. The peak in the beta$_2$ band at 80 min is a result of artefact. This plot shows that, although the absolute power in the delta band decreased with time, the relative contribution to total power remained very constant.

induction values. Delta power also decreased but always remained considerably greater than its pre-induction value. The relative contribution of the power in the delta band to total power remained constant until the onset of cardiopulmonary bypass (fig. 7). The relative contribution to total power from the other bands decreased and then remained constant at a very low level.

After direct questioning, no patient reported any awareness during the operation. The first memory after surgery, in all patients, was of being in the intensive care unit.

DISCUSSION

The electroencephalographic effects of small doses of fentanyl and sufentanil (fentanyl 0.4–0.6 mg, sufentanil 0.04–0.06 mg, total doses) have been studied in man in combination with droperidol 15–20 mg and nitrous oxide by Kubicki and colleagues (1977). The only significant change they found was an increase in delta power by a factor of 10. The electroencephalographic effects of higher doses of fentanyl (30–70 $\mu g\,kg^{-1}$ with and without nitrous oxide) were investigated by us in a previous study (Sebel et al., 1981b) in which it was observed that fentanyl 50–70 $\mu g\,kg^{-1}$ produced a characteristic e.e.g. response; a massive increase in delta power. Fentanyl 30 $\mu g\,kg^{-1}$ produced a different e.e.g. pattern with less delta activity and was clinically inadequate as an anaesthetic. Nitrous oxide did not affect the electroencephalographic responses to fentanyl and from the electroencephalographic standpoint does not appear to be a necessary component of an opioid anaesthetic technique. For this reason, and the fact that nitrous oxide may cause cardiovascular depression in combination with an opioid analgesic (McDermott and Stanley, 1974; Lunn et al., 1979) nitrous oxide was not used in this study.

The e.e.g. responses to sufentanil 15 $\mu g\,kg^{-1}$ are indistinguishable from those seen after fentanyl 50–70 $\mu g\,kg^{-1}$. This is in keeping with the similarity in the pharmacological profiles of the two compounds. The decrease in total power in the e.e.g. with respect to time was also seen with fentanyl. The constancy of the delta band contribution to total power suggests that this may be useful as an index of anaesthetic depth during opioid anaesthesia, and is worthy of further study in a situation where the e.e.g. is not affected by cardiopulmonary bypass. Another way of using the e.e.g. as a guide to the depth of anaesthesia would be to look at the recovery of the higher frequency activity. It is not yet clear how the e.e.g. varies during the recovery period, but initial results suggested that power in the higher (beta) frequency bands may increase linearly with respect to time. Unexpectedly, a similar response was not seen in the delta band. Although delta power decreased during the first 3–4 h after operation, sporadic increases then occurred during the next few hours. These may result from the recurrence of episodes of a natural non-REM sleep pattern, which is also characterized by high powered delta activity (Sebel, P. S. and Bovill, J. G., unpublished observations).

During arousal from sleep, the e.e.g. changes from high voltage slow waves to low voltage fast waves and such an e.e.g. response has been demonstrated following skin incision during halothane anaesthesia in adult man (Oshima, Shirgu and Mori, 1981). This suggests that reappearance of fast wave activity in response to a specific stimulus may be an indication that anaesthesia is becoming "light". There were no e.e.g. responses to the stimuli of intubation or surgery in any patient in this study or during the investigation under fentanyl anaesthesia (Sebel et al., 1981b). This may indicate that opioid analgesics are more effective than inhalation agents in blocking cortical arousal during surgery.

The sharp waves seen after sufentanil are similar to those we have described after the administration of fentanyl (Sebel et al., 1918b). They do not resemble epileptic spike waves and never became generalized, nor were they associated with any clinical signs of epileptic activity. Their neurophysiological significance remains uncertain. Similar sharp waves have been described in dogs following the administration of opioid analgesics (Wauquier et al., 1981), and after the injection of β-endorphin into the cerebral ventricles of rats (Havlicek et al., 1980).

We conclude that sufentanil anaesthesia produced an e.e.g. response characterized by high voltage slow delta waves. This response is similar to that produced by high-dose fentanyl anaesthesia.

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EFFETS ELECTROENCEPHALOGRAPHIQUES DE L'ANESTHESIE AU SUFENTANIL CHEZ L'HOMME

RESUME

Les effets de l'anesthésie provoquée par $15\,\mu g\,kg^{-1}$ de sufentanil, l'air et l'oxygène sur l'electroencéphalogramme ont été étudiés sur 12 patients, avant et après une dérivation cardiopulmonaire. Les réactions à l'e.e.g. ont été caractérisées par des ondes delta lentes à haute tension. Bien que la puissance moyenne de la bande delta ait diminué avec le temps, la contribution de la puissance totale dans la plage des fréquences 0,5–40 Hz est restée constante jusqu'au début de la dérivation cardiopulmonaire. On a vu des ondes accentuées d'une signification neurophysiologique incertaine. Elles n'ont pas été associées aux signes cliniques d'une activité épileptique. On pourrait envisager d'utiliser les réactions à l'e.e.g. pour la surveillance de la profondeur de l'anesthésie pendant toute la durée d'une anesthésie basée sur de fortes doses de substances opiacées.

ELEKTROENZEPHALOGRAPHISCHE AUSWIRKUNGEN EINER SUFENTANIL-ANÄSTHESIE BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Auswirkungen einer Sufentanil-Anästhesie $15\,\mu g\,kg^{-1}$ mit Luft und Sauerstoff auf das Elektroenzephalogramm wurden bei 12 Patienten vor und nach der pneumokardialen Überbrückungschirurgie studiert. Die E.e.g.-Reizbeantwortungen zeichneten sich durch langsame Delta-Wellen mit hoher Spannung aus. Obwohl das mittlere Potential in der Delta-Bandbreite mit der Zeit nachliess, blieb der Beitrag des Delta-Potentials zum Gesamtpotential im Frequenzbereich 0.5–40 Hz bis zum Einsetzen der pneumokardialen Überbrückung konstant. Spitze Wellen von ungewisser neurophysiologischer Bedeutung wurden beobachtet. Diese waren mit klinischen Anzeichen epileptischer Aktivität nicht verbunden. Die Anwendung der E.e.g.-Reizbeantwortungen zur Überwachung der Tiefe einer durch hohe Dosen von Opiaten hervogerufenen Anästhesie könnte in Zukunft Wirklichkeit werden.

EFECTOS ELECTROENCEFALOGRAFICOS DE LA ANESTESIA MEDIANTE SUFETANILO EN EL HOMBRE

SUMARIO

Se estudiaron en 12 pacientes los efectos de la anestesia efectuada con $15\,\mu g\,kg^{-1}$ de sufentanilo, aire y oxígeno, en el electroencefalograma, antes y después de llevar a cabo una desviación cardiopulmonar. Las respuestas del e.e.g. se caracterizaron por ondas delta, lentas y de alto voltaje. Aunque la potencia media en la banda delta declinó con el paso del tiempo, la contribución de la potencia delta a la potencia total, en la gama de 0,5 a 40 Hz, permaneció constante hasta el comienzo de la desviación cardiopulmonar. Se contemplaron ondas muy agudas cuyo significado neurofisiológico es incierto. Estas no vinieron asociados con signos clínicos de actividad epiléptica. Puede que llege a ser posible usar la respuesta del e.e.g. cual un monitor de la "profundidad de la anestesia" durante aquella efectuada con grandes dosis de opioides.

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ANTAGONISM OF ORG NC45 (VECURONIUM) AND PANCURONIUM NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE

P. J. GENCARELLI AND R. D. MILLER

SUMMARY

The antagonism, by neostigmine, of neuromuscular blockade produced by either Org NC45 or pancuronium was studied in 29 anaesthetized patients during a continuous infusion of the myoneural blocker. The ED_{50} of neostigmine (dose which produced a 50% antagonism) when antagonizing Org NC45 and pancuronium was 0.011 mg kg^{-1} and 0.010 mg kg^{-1} respectively. The dose–response relationships for the antagonism of Org NC45 and pancuronium neuromuscular blockades were not significantly different. The duration of the effect of neostigmine was not different when antagonizing an Org NC45- or pancuronium-induced blockade. We concluded that Org NC45 and pancuronium are effectively and equally (independent of their pharmacokinetics) antagonized by neostigmine in man.

Org NC45 (new generic name, vecuronium), a homologue of pancuronium, is a new, short acting, non-depolarizing neuromuscular blocking agent. In animal studies, neuromuscular blockade induced by Org NC45 was antagonized easily by acetylcholinesterase inhibitors and aminopyridines (Marshall et al., 1980). A comparative study in rats showed no difference in the amount of neostigmine required to antagonize the neuromuscular blockade produced by either pancuronium or Org NC45 (Booij et al., 1980) yet, in man, Fahey and others (1981b) found that less neostigmine was required to antagonize an Org NC45 neuromuscular blockade as compared with that required to antagonize blockade from pancuronium. However, as this analysis was made during a changing neuromuscular blockade we have re-evaluated the ability of neostigmine to antagonize an Org NC45- or pancuronium-induced neuromuscular blockade using a steady-state infusion technique.

PATIENTS AND METHODS

Twenty-nine adult patients were studied. Their mean age (±1 SD) and body weight were 41 ± 15 yr and 70.2 ± 15.8 kg respectively. Informed consent was granted by each patient for participation in the study according to the guidelines of the University of California, San Francisco's Committee on Human Research. One hour after receiving diazepam 10–20 mg by mouth, anaesthesia was induced with thiopentone 1–3 mg kg^{-1} i.v., halothane and 60% nitrous oxide in oxygen and maintained with halothane 0.4–1.2% end-tidal concentration (as determined by mass spectrometry) and 60% nitrous oxide in oxygen. Endotracheal intubation was accomplished without the use of neuromuscular blockade. Ventilation was controlled to maintain an end-tidal $P\text{CO}_2$ of 3.99–5.32 kPa. Oesophageal temperature was maintained between 34.5 and 36.0 °C with a warming blanket.

A Grass S-44 stimulator was used to apply supramaximal square-wave bipolar pulses of 0.15 ms duration and 0.15 Hz to thin-wall 27-gauge steel needle electrodes placed 2–3 cm apart near the ulnar nerve on the wrist. The resultant adduction of the thumb was measured by a force displacement transducer (Grass FT-10) and recorded continuously on a polygraph.

After at least 30 min of anaesthesia, either pancuronium ($n = 14$) or Org NC45 ($n = 15$) was infused continuously from a Harvard Apparatus Infusion pump to maintain a constant 90% depression of twitch tension. When the required infusion rate and depression of twitch tension were constant for at least 15 min, a randomly selected dose of neostigmine was given as an i.v. bolus during the continuous infusion. The required infusion rates for pancuronium and Org NC45 were 0.41 ± 0.18 μg min^{-1} (mean ± SD) and 1.08 ± 0.67 μg min^{-1} respectively. The doses of neostigmine administered to the patients receiving Org NC45 were 0.005 mg kg^{-1} ($n = 3$),

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0.01 mg kg^{-1} ($n = 5$), 0.02 mg kg^{-1} ($n = 4$) and 0.03 mg kg^{-1} ($n = 3$). The doses of neostigmine for the patients receiving pancuronium were 0.005 mg kg^{-1}, ($n = 5$), 0.01 mg kg^{-1} ($n = 5$) and 0.03 mg kg^{-1} ($n = 4$). The 0.02 mg kg^{-1} dose of neostigmine was omitted in the pancuronium group because it was not required to define the neostigmine dose–response curve. Each patient was studied only once and received only one dose of neostigmine. The resultant maximum antagonism of twitch depression was noted (here presented as a percentage of the pre-existing value of twitch depression). Times from the injection of neostigmine to 50 and 100% of peak effect and 75 and 50% return to relaxant depressed twitch tension were calculated. This technique has been described in more detail by Miller and colleagues (1974).

The dose–response curves for neostigmine when antagonizing either pancuronium or Org NC45 were calculated by analysis of linear regression on a semi-logarithmic scale. The dose–response and duration–effect data were compared by analysis of covariance (Snedecor and Cochran, 1967). Statistically significant differences were assumed at $P<0.05$.

RESULTS

The ED_{50} of neostigmine (the doses of neostigmine which produced a 50% antagonism) when antagonizing Org NC45 and pancuronium were 0.011 mg kg^{-1} and 0.010 mg kg^{-1} respectively (fig. 1). The regression coefficients of the neostigmine dose–response linear regressions for Org NC45 and pancuronium on the semi-logarithimic plot were 76.4 and 72.9; the common regression coefficient of the data was 74.05. The neostigmine dose–response curves for the antagonism of neuromuscular blockade produced by Org NC45 and pancuronium were not significantly different.

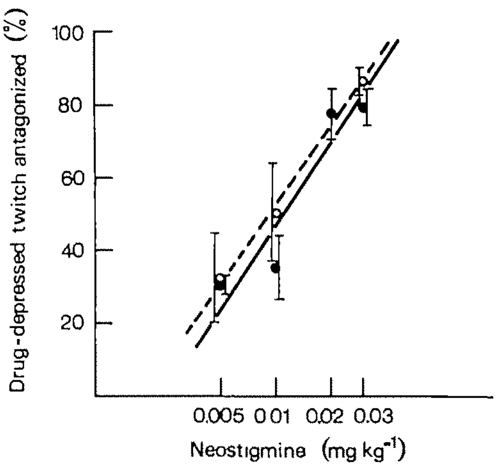

FIG. 1. Relationship between dose of neostigmine and percentage of either the Org NC45- or pancuronium-depressed twitch antagonized in patients (mean ± SEM). The lines represent linear regression analyses. ●——● = Org NC 45; o---o = pancuronium.

The duration of the effect of neostigmine was not different when antagonizing an Org NC45 or pancuronium neuromuscular blockade (fig. 2).

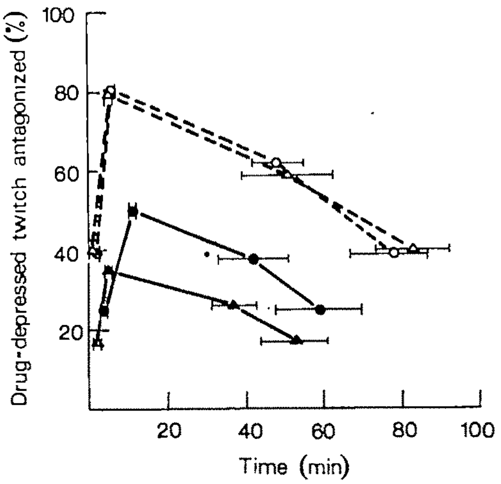

FIG. 2. Plot of time and percentage of either the Org NC45- or pancuronium-depressed twitch antagonized by neostigmine 0.01 mg kg^{-1} or 0.03 mg kg^{-1} (mean ± SEM). Org NC45: △---△ = neostigmine 0.03 mg kg^{-1}, ▲——▲ = neostigmine 0.01 mg kg^{-1}. Pancuronium: o---o = neostigmine 0.03 mg kg^{-1}, ●——● = neostigmine 0.01 mg kg^{-1}.

The time from injection to peak effect of neostigmine 0.01 mg kg^{-1} was shorter when antagonizing Org NC45 (5.3 min) than pancuronium (10.7 min). However, the times to peak effect were not different with neostigmine 0.03 mg kg^{-1}.

DISCUSSION

The similarity of neostigmine dose and effect on the neuromuscular blockades produced by Org NC45 and pancuronium in animals (Booij et al., 1980; Durant, Houwertjes and Crul, 1980) is in accord with our results. Yet in man, Fahey and colleagues (1981b) found that less neostigmine was required to antagonize an Org NC45- as compared with a pancuronium-induced neuromuscular blockade. This apparent discrepancy may be explained by differences in experimental methods and the dissimilarity of the pharmacokinetics of Org NC45 and pancuronium. The neuromuscular block of Org NC45 has a shorter duration of action and faster rate of recovery than the blockade from pancuronium (Van der Veen and Bencini, 1980) probably because Org NC45 has a shorter elimination half-life (Fahey et al., 1981a). Moreover, Fahey and co-workers (1981b) administered intermittent boluses of neostigmine with an initial 95% twitch depression from Org NC45 without compensation for the different pharmacokinetics and durations of action of Org NC45 and pancuronium. Under such circumstances, neuromuscular blockade from Org NC45 would decrease more quickly than blockade from pancuronium and hence contribute to the apparently enhanced effect. However, in our study, the differences in Org NC45 and pancuronium pharmacokinetics and the durations of neuromuscular blockade were obviated by the use of a continuous infusion of the neuromuscular blockers which was adjusted to achieve equal and unchanging depression of twitch tension. We conclude that Org NC45 and pancuronium are effectively and equally (independent of their different pharmacokinetics and durations of effect) antagonized by neostigmine in man.

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ANTAGONISME DE L'ORG NC45 (NORCURON) ET DU PANCURONIUM DANS LE BLOCAGE NEUROMUSCULAIRE PAR LA NEOSTIGMINE

RESUME

Chez 29 patients anesthésiés au cours d'une infusion continue d'agent de blocage myoneural, on a étudié l'antagonisme de la néostigmine vis-à-vis du blocage neuromusculaire produit soit par l'Org NC45 soit par le pancuronium. L'ED_{50} de la néostigmine (dose qui produisait un antagonisme de 50%) pour antagoniser l'Org NC45 et le pancuronium était de $0{,}011\ \mathrm{mg\,kg^{-1}}$ et de $0{,}010\ \mathrm{mg\,kg^{-1}}$, respectivement. Les rapports dose–résponse pour l'antagonisme des blocages neuromusculaires de l'Org NC45 et du pancuronium n'étaient pas sensiblement différents. La durée de l'effet de la neostigmine n'était pas différente lorsque cette substance antagonisait le blocage obtenu par l'Org NC45 ou par le pancuronium. Nous en concluons que l'Org NC45 et le pancuronium sont effectivement et également antagonisés par la néostigmine chez l'homme (indépendamment de leur pharmacocinétique).

GEGENWIRKUNG AUF ORG NC45 (NORCURON) UND PANCURONIUM ALS NEUROMUSKULÄRE BLOCKIERUNG DURCH NEOSTIGMIN

ZUSAMMENFASSUNG

Die Neostigmin-Gegenwirkung auf neuromuskuläre Blockierung entweder durch Org NC45 oder Pancuronium wurde bei 29 narkotisierten Patienten während kontinuierlicher Infusion des Blockierungsmittels untersucht. Das ED_{50} von Neostigmin (die Dosis, die einen 50%igen Antagonismus bewirkte) war bei der Gegenwirkung auf Org NC45 und Pancuronium $0{,}011\ \mathrm{mg\,kg^{-1}}$ und $0{,}010\ \mathrm{mg\,kg^{-1}}$. Das Dosis-Reaktionsverhältnis für die Aufhebung neuromuskulärer Blockierungen bei Org NC45 und bei Pancuronium zeigt keinen signifikanten Unterschied bei den beiden Drogen nicht besonders unterschiedlich. Die Wirkungsdauer von Neostigmin war ebenfalls bei beiden Narkosemitteln nicht unterschiedlich. Wir schliessen daraus, dass diese beiden Narkosemittel wirksam und gleichermassen (unabhängig von ihrer Pharmakokinetik) durch Neostigmin antagonisiert werden.

ANTAGONISMO DEL ORG NC45 (NORCURON) Y DEL PANCURONIO EN EL BLOQUEO NEUROMUSCULAR POR NEOESTIGMINA

SUMARIO

Se estudió en 29 pacientes anestesiados durante la infusión continua del bloqueador mioneural, el antagonismo por la neoestigmina en el bloqueo neuromuscular producido tanto por el Org NC45 como por el pancuronio. El ED_{50} de neoestigmina (dosis que produce un antagonismo del 50%) al antagonizar el Org NC45 y el pancuronio era de 0,011 mg kg^{-1} y de 0,010 mg kg^{-1}, respectivamente. Las relaciones dosis–respuesta para el antagonismo del bloqueo neuromuscular por Org NC45 y pancuronio no variaban de manera significante. La duración del efecto de la neoestigmina no era distinto cuando antagonizaba un bloqueo inducido por Org NC45 o por pancuronio. Sacamos la conclusión de que la neoestigmina antagoniza igual y efectivamente tanto el Org NC45 como el pancuronio en el hombre (independientemente de su farmacocinética).

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EFFECT OF HYPOCARBIA AND HYPERCARBIA ON THE ANTAGONISM OF PANCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE WITH NEOSTIGMINE IN MAN

K. WIRTAVUORI, M. SALMENPERÄ AND T. TAMMISTO

SUMMARY

The effects of variations in carbon dioxide concentration on the antagonism of pancuronium-induced neuromuscular block by neostigmine were studied in 21 patients: normocarbia ($P_{E'_{CO_2}}$ 5.4%, Pa_{CO_2} 4.93 kPa, $n=7$), hypocarbia ($P_{E'_{CO_2}}$ 3.6%, Pa_{CO_2} 3.30 kPa, $n=7$) and hypercarbia ($P_{E'_{CO_2}}$ 7.5%, Pa_{CO_2} 7.13 kPa, $n = 7$). Mechanical and electromyographic responses to ulnar nerve stimulation (0.1 Hz and 2 Hz) were recorded. A 90% block during nitrous oxide in oxygen anaesthesia was maintained by incremental single injections of pancuronium and reversed with neostigmine 0.035 mg kg^{-1} with atropine 0.0175 mg kg^{-1}. The recovery of twitch tension up to 50% was similar in all groups but thereafter slower in the hypercarbia group. The recovery times from 25% to 75% twitch tension correlated with Pa_{CO_2} ($r=0.55$, $P<0.05$). A residual block of about 10% was seen in hypercarbic patients. However, the recovery of e.m.g. amplitude and train-of-four ratios was similar in all groups. Thus, the impaired recovery of twitch tension seems to be the result of depressed contractility rather than failure of neuromuscular transmission.

Residual neuromuscular blockade is considered to contribute significantly to morbidity and possibly even mortality following operation (Cascorbi and Gravenstein, 1974). Factors which impair recovery from neuromuscular blockade include alterations in pH, and metabolic acidosis has been claimed to cause a state of neostigmine-resistant curarization (Feldman, 1979). It has been shown that blockade by tubocurarine and pancuronium cannot be antagonized fully in the presence of hypercarbia (Miller et al., 1975; Miller and Roderick, 1978). In addition, hypercarbia can attenuate the twitch response to nerve stimulation during blockade with tubocurarine (Katz and Wolf, 1964) and impede recovery from blockade with pancuronium (Norman, Katz and Seed, 1970). However, the role of these factors in association with the degree of hypercarbia likely to be encountered in clinical practice during the reversal of blockade does not seem to have been established in man. Therefore the recovery of neuromuscular transmission during the reversal of blockade with neostigmine was studied under conditions of moderate hypercarbia and moderate hypocarbia.

PATIENTS AND METHODS

Twenty-one patients (23–59 yr) in good general health and undergoing varicose vein surgery lasting less than 1 h participated in the study. Consent for the study was obtained from each patient. They were matched by sex, age, weight and height into three groups of seven patients (table I). Each patient was premedicated with oxycodone 1.4 mg per 10 kg i.m., promethazine 25–50 mg i.m. and atropine sulphate 0.1 mg per 10 kg i.m. 30 min before the induction of anaesthesia. Fentanyl 0.05–0.1 mg was administered i.v. and followed by thiopentone 200–400 mg i.v. Tracheal intubation was facilitated with suxamethonium 0.7 mg kg^{-1} and, after full recovery of twitch tension, pancuronium 0.05 mg kg^{-1} i.v. was given as an initial single injection and in incremental doses to achieve and maintain a twitch suppression of about 90%. The lungs were ventilated mechanically with nitrous oxide in oxygen with an average oxygen concen-

TABLE I. *Patient data in the groups studied (mean ± SEM)*

Group	M/F	Age (yr)	Weight (kg)	Height (cm)
Normocarbia	2/5	42.4 ± 5.0	68.1 ± 6.5	166 ± 3.0
Hypocarbia	1/6	39.3 ± 3.7	63.6 ± 3.8	170 ± 2.7
Hypercarbia	1/6	36.3 ± 3.4	65.7 ± 3.3	168 ± 1.4

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tration of 30% as measured with a polarographic sensor. Fentanyl was administered in doses of 0.05–0.1 mg to provide analgesia when required.

The minute ventilation was adjusted to produce end-tidal carbon dioxide concentrations of about 3.5, 5.5 or 7.5% by varying the respiratory rates, the tidal volumes remaining constant. At the end of the operation the 90±2% neuromuscular blockade was reversed with neostigmine 0.035 mg kg^{-1} combined with atropine 0.0175 mg kg^{-1} i.v. A sample for blood-gas analysis was drawn from the radial artery just before the administration of the neostigmine. During reversal ventilation remained unchanged.

The ulnar nerve was stimulated through steel needle electrodes near the wrist with 0.1 Hz supramaximal square-wave stimuli of 0.1 ms duration. In addition, train-of-four stimuli at 2 Hz were given after recovery of the twitch height to a plateau—a state of no change of twitch height over 2 min. Mechanical myographic (m.m.g.) responses (the isometric tension produced by thumb adduction) were measured with a force transducer and the corresponding electromyogram (e.m.g.) was recorded through a 0.35-mm × 15-mm (27-gauge) needle electrode located in the adductor pollicis muscle. The calibration of the force and e.m.g. measurements was performed for each patient after induction of anaesthesia (thiopentone–fentanyl–nitrous oxide) and before the administration of suxamethonium.

For statistical comparisons Student's *t* test, Mann–Whitney test and linear regression analysis were used. $P < 0.05$ was considered significant.

RESULTS

Mean Pa_{CO_2} and pH values for the three groups of patients are shown in table II. The normocarbic group differred significantly from its hypocarbic and hypercarbic counterparts. The pH values correlated well with the corresponding carbon dioxide values, and no metabolic compensation was observed during anaesthesia. The amount of pancuronium administered to maintain 90% twitch suppression was slightly greater ($P < 0.2$) in the hypocarbic group than in the normocarbic or hypercarbic groups (table II). The duration of 10% twitch tension was comparable in all groups (table II).

The initial recovery to 50% twitch tension took about 3 min in all groups (fig. 1). Thereafter, recovery was slower in the hypercarbic group. In the normocarbic and hypocarbic groups the recovery was similar up to 90% twitch tension at 9 min, and from which point it seemed slightly faster in the hypocarbic group, but no statistical significance was reached.

The recovery time from 25% to 75% twitch tension correlated with arterial $P\text{CO}_2$ ($r = 0.55$, $P < 0.05$) although the scatter was wide (fig. 2). The means of the peak recovery values of twitch tension, e.m.g. amplitude and the corresponding train-of-four ratios achieved in the three groups are summarized in figure 3. Twitch tension recovered to slightly more than its initial value in the hypocarbic and normocarbic groups, but in

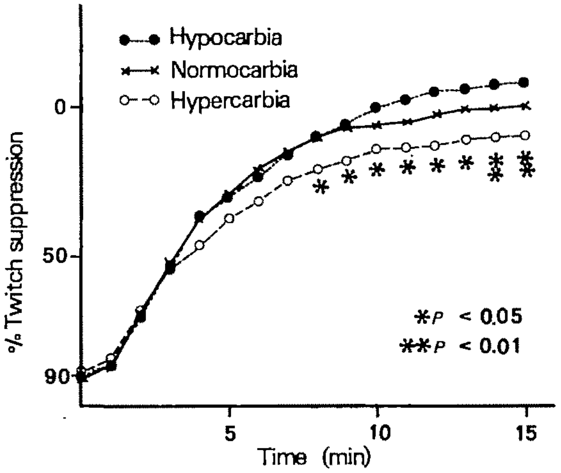

FIG. 1. Recovery of mechanical myographic twitch tension in the three groups. Neostigmine administered at 0 min. (*P* values, Mann–Whitney tests.)

TABLE II. *End-tidal carbon dioxide (%), Pa_{CO_2}, pH, dose of pancuronium and duration of 10% twitch tension in the three groups (mean ± SEM)*

Group	End-tidal CO_2	Pa_{CO_2} (kPa)	pH	Total pancuronium (μg kg^{-1} min^{-1})	Duration of 10% twitch tension (min)
Normocarbia	5.4	4.94±0.15	7.41±0.01	1.83±0.26	40.6±4.1
Hypocarbia	3.6	3.30±0.17	7.55±0.02	2.18±0.23	37.4±4.9
Hypercarbia	7.5	7.13±0.20	7.28±0.01	1.80±0.16	42.6±3.8

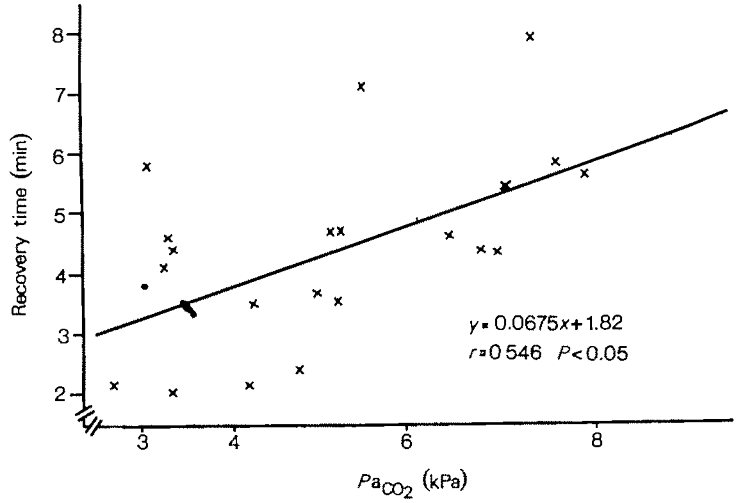

FIG. 2. Correlation between time of recovery (min) from 25% to 75% twitch tension and arterial carbon dioxide tension. $r=0.55$, $P<0.05$.

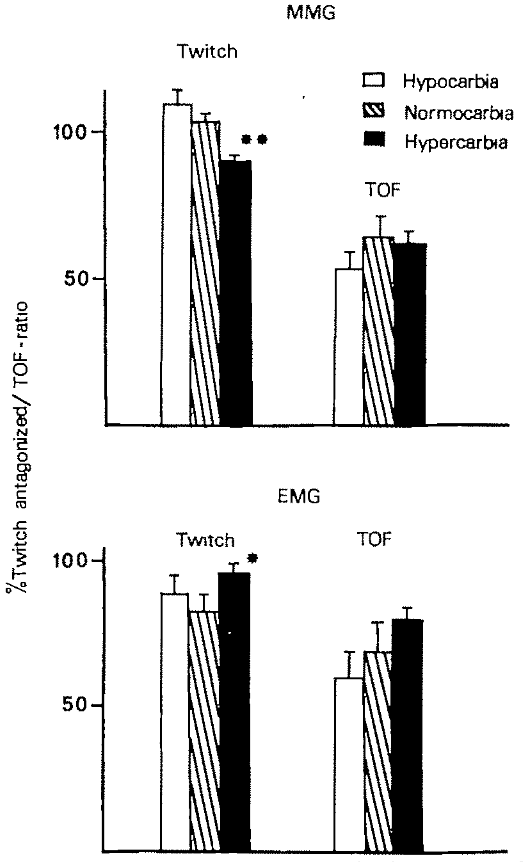

FIG. 3. Peak recovery values of mechanical myographic (MMG) twitch tension and electromyographic (EMG) amplitudes and corresponding train-of-four (TOF) ratios (mean ± SEM). $*P<0.05$; $**P<0.001$.

the hypercarbic group a 10% residual effect persisted ($P<0.001$). The mechanical myograph train-of-four ratios were similar in all groups and amounted to about 60%. The recovery of e.m.g. amplitude (0.1 Hz) seemed to be better in the hypercarbic group (mean 96.4±3.0%) than in the normocarbic group (83.4±5.7% $P<0.05$), and was intermediate in hypocarbia (89.1±7.2). There were no significant differences between the e.m.g. train-of-four ratios during reversal (2 Hz) (79.9±3.1% in hypercarbia, 68.4±11.1% in normocarbia and 61.0±10.1% in hypocarbia).

DISCUSSION

Hypercarbia has been shown to attenuate the twitch response to nerve stimulation during blockade with tubocurarine in man (Katz and Wolf, 1964). This has not been as clearly demonstrated with pancuronuim and could be a result of the different ionization behaviour of these two drugs at physiological pH (Feldman, 1979). Norman, Katz and Seed (1970) showed that spontaneous recovery from pancuronium blockade was slower when hypercarbia was induced in previously hyperventilated patients and that the recovery was faster with overventilation after hypercarbia. Crul-Sluijter and Crul (1974) found that pancuronium blockade was potentiated by metabolic and respiratory acidosis in cats *in vivo* and in the rat phrenic nerve–diaphgram preparation *in vitro*. Based on their findings in cats, Miller and Roderick (1978) concluded that hypercarbia prevents the antagonism of pancuronium by neostigmine.

The contribution of these slight changes in the stimulation-evoked responses to overall clinical blockade is probably insignificant during the maintenance of anaesthesia. However, during recovery from blockade and anaesthesia, hypercarbia could precipitate a vicious circle of residual neuromuscular blockade, progressive hypoventilation and increasing carbon dioxide tension. The impairment of the response to neostigmine in the presence of hypercarbia could be of even more importance.

In this study moderately hyperventilated patients showed a tendency to consume more pancuronium than their hypoventilated or normoventilated counterparts, although the trend was small, when the myoneural blocking drug was administered in such a way as to maintain constant twitch depression. Since increasing the amounts of blocker is known to decrease the recovery of twitch height, the more rapid recovery of twitch tension in hyperventilated patients than in hypoventilated patients might have been more pronounced had the doses of pancuronium been identical.

The decrease in the mechanical twitch response following neostigmine in the hypoventilated patients was not seen in the measurements of e.m.g. amplitude. This finding was interpreted as evidence for the direct depressant effects of carbon dioxide tension on contractility. E.m.g. amplitude has been claimed to be a better indicator of actual neuromuscular blockade than measurements of twitch tension (Lee and Katz, 1980).

A train-of-four ratio greater than 70% is thought to correlate with clinical tests of the adequacy of reversal (Ali and Savarese, 1976). Using electromyography, a train-of-four ratio of 75% correlates with adequate clinical recovery (Ali and Savarese, 1976). The similarity of the train-of-four ratios after recovery in the present patient groups suggested that hypercarbia did not induce failure of neuromuscular transmission but rather affected contractility. This is supported by the fact that none of our patients showed signs of residual muscle weakness by the standard clinical criteria, which suggests that the depression of contractility brought about by clinically acceptable hypercarbia is well tolerated in the presence of intact neuromuscular transmission.

The mechanism of the decrease in twitch tension in hypercarbia is not clear, but seems also to apply to heart muscle. A decrease of about 30% in the isometric contraction force of the isolated papillary muscle of a cat's heart related to $P\text{CO}_2$ has been demonstrated when the concentration of carbon dioxide was increased from 4.7% to 9.8% (Foëx, 1980). Secondary changes in extracellular pH or ions might be mediators of the effect.

In conclusion, clinically relevant moderate hypercarbia impaired the recovery of twitch tension in anaesthetized patients after neostigmine had been used to antagonize pancuronium blockade. However, no impairment of recovery was demonstrated in e.m.g. or in train-of-four ratios which probably reflect better the functioning of the neuromuscular junction. Thus the hypercarbia-induced decrease in twitch tension seemed to be the result of depressed contractility rather than of neuromuscular blockade. Since proper functioning of the neuromuscular junction probably contributes more to restitution of adequate muscle tone than slight changes in contractility, the clinical significance of moderate hypercarbia is questionable.

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EFFET DE L'HYPOCARBIE ET DE L'HYPERCARBIE SUR L'ANTAGONISME PAR LA NEOSTIGMINE D'UN BLOCAGE NEUROMUSCULAIRE PROVOQUE PAR LE PANCURONIUM CHEZ L'HOMME

RESUME

Les effets des variations dans la concentration de gaz carbonique sur l'antagonisme par la néostigmine d'un blocage neuromusculaire provoqué par le pancuronium ont fait l'objet d'une étude portant sur 21 patients et couvrant: normocarbie ($P\mathrm{E}'_{CO_2}$ 5,4%, Pa_{CO_2} 4,93 kPa, $n = 7$) hypocarbie ($P\mathrm{E}'_{CO_2}$ 3,6%, Pa_{CO_2} 3,30 kPa, $n = 7$) et hypercarbie ($P\mathrm{E}'_{CO_2}$ 7,5%, Pa_{CO_2} 7,13 kPa, $n = 7$). Nous avons enregistré les réactions mécaniques et électromyographiques à la stimulation du nerf ulnaire (0,1 Hz et 2 Hz). Un blocage à 90% pendant une anesthésie au protoxyde d'azote dans l'oxygène a été maintenu à l'aide d'injections uniques croissantes de pancuronium, puis inversé à l'aide de néostigmine à raison de 0,035 mg kg^{-1} et d'atropine administrée à raison de 0,0175 mg kg^{-1}. La récupération de la tension de la contraction jusqu'à 50% a été similaire dans tous les groupes, mais au-delà de ce chiffre elle a été plus lente dans le groupe hypercarbie. Les temps nécessaires à la récupération compris entre 25% et 75% de la tension de la contraction ont été en corrélation avec la Pa_{CO_2} ($r = 0.55$, $P < 0.05$). Un blocage résiduel d'environ 10% a été constaté chez les patients du groupe hypercarbie. Quoi qu'il en soit, la récupération de l'amplitude de l'e.m.g et des rapports de la chaîne de quatre a été similaire dans tous les groupes. Ainsi, l'altération de la récupération de la tension de la contraction semble être le resultat d'une contractilité déprimée plutôt que d'une défaillance de la transmission neuromusculaire.

DIE AUSWIRKUNG VON HYPOKAPNIE UND HYPERKAPNIE AUF DIE BEKÄMPFUNG EINER MIT PANCURONIUM INDUZIERTEN NEUROMUSKULÄREN BLOCKADE MITTELS NEOSTIGMIN

ZUSAMMENFASSUNG

Die Auswirkungen von Änderungen der Kohlendioxidkonzentrationen auf die Bekämpfung von einer pancuronium-induzierten neuromuskulären Blockade mittels Neostigmin wurde bei 21 Patienten studiert: Normakapnie ($P\mathrm{E}'_{CO_2}$ 5,4%, Pa_{CO_2} 4,93 kPa, $n = 7$), Hypokapnie ($P\mathrm{E}'_{CO_2}$ 3,6%, Pa_{CO_2} 3,30 kPa, $n = 7$) und Hyperkapnie ($P\mathrm{E}'_{CO_2}$ 7,5%, Pa_{CO_2} 7,13 kPa, $n = 7$). Mechanische und elektromyographische Reaktionen auf Reizungen des Ellennervs (0,1 und 2 Hz) wurden ermittelt. Eine 90% Blockade während einer Anästhesie mit Lachgas in Sauerstoff wurde mittels gestufter einzelner Injektioner von Pancuronium aufrechterhalten und mittels Neostigmin 0,035 mg kg^{-1} und Atropin 0,0175 mg kg^{-1} umgekehrt. Die Erholung der Zuckungsspannung bis zu 50% war bei allen Gruppen ähnlich, aber ging danach bei der Hyperkapnie-gruppe langsamer vor sich. Die Erholungszeiten von 25% auf 75% Zuckungsspannung zeigten eine Korrelation zu Pa_{CO_2} ($r = 0,55$, $P < 0,05$). Eine Restblockade von ca 10% wurde bei Hyperkapnie Patienten beobachtet. Die Erholung der emg-Amplitude und Viererzugverhältnisse war jedoch bei allen Gruppen ähnlich. Die beeinträchtigte Erholung der Zuckungsspannung scheint eher das Ergebnis von herabgedrückter Kontraktilität als das Ergebnis eines Versagens von neuromuskulärer Übertragung zu sein.

EFECTO DE LA HIPERCARBIA Y DE LA HIPOCARBIA EN EL CONTRARRESTO MEDIANTE NEOSTIGMINA DEL BLOQUEO NEUROMUSCULAR INDUCIDO POR PANCURONIO

SUMARIO

Se estudiaron en 21 pacientes con normocarbia ($P\mathrm{E}'_{CO_2}$ al 5,4%, Pa_{CO_2} 4,93 kPa, $n = 7$) hipocarbia ($P\mathrm{E}'_{CO_2}$ al 3,6% Pa_{CO_2} 3,30 kPa, $n = 7$), e hipocarbia ($P\mathrm{E}'_{CO_2}$ al7,5%, Pa_{CO_2} 7,13 kPa, $n = 7$), los efectos de las variaciones en la concentración de dióxido de carbono al contrarrestar, mediante neostigmina, el bloqueo neuromuscular inducido por pancuronio. Se registraron las respuestas mecánicas y electromiográficas a la estimulación del nervio cubital (0,1 Hz y 2 Hz). Se mantuvo un bloqueo del 90% durante la anestesia con óxido nitroso en óxigeno, incrementando las inyecciones unitarias de pancuronio y contrarrestándolas y con 0,035 mg kg^{-1} de neostigmina con 0,0175 mg kg^{-1} de atropina. La recuperación de hasta el 50% de la tensión de contracción fue similar en todos los grupos pero más lenta posteriormente en el grupo con hipercarbia. Los tiempos de recuperación correspondientes a la tensión de contracción de entre el 25% y el 75% vinieron correlacionados con Pa_{CO_2} ($r = 0,55$ $P < 0,05$). En los pacientes hipercárbicos se contempló un bloqueo residual de aproximadamente el 10%. No obstante, la recuperación de los regímenes de amplitud y de los tres de cuatro impulsos fue similar en todos los grupos. De este modo, parece que la dificultad en la recuperación de la tensión de contracción es consecuencia de contractabilidad deprimida y no de fallo alguno en la transmisión neuromuscular.

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ANTAGONISM OF PANCURONIUM IN RENAL FAILURE: NO RECURARIZATION

D. R. BEVAN, D. ARCHER, F. DONATI, A. FERGUSON AND B. D. HIGGS

SUMMARY

Neuromuscular transmission was measured using train-of-four stimulation, during and after anaesthesia, in 20 patients with end-stage renal failure. Neuromuscular blockade was provided with pancuronium in single doses of either 3 or 6 mg per 70 kg, and antagonized at 10% recovery with atropine and neostigmine 2.5 mg per 70 kg. Reversal was followed by progressive recovery of muscle twitch in every patient during the 3 h of the study. Recovery was more rapid after the smaller dose of pancuronium and was inversely correlated with the duration of blockade. It is concluded that, when pancuronium is antagonized with neostigmine in patients with renal failure, neuromuscular transmission recovers without evidence of recurarization. However, when large doses of pancuronium are antagonized with neostigmine 2.5 mg, recovery may be insufficient to ensure normal ventilatory function.

The use of non-depolarizing neuromuscular blocking drugs in patients with renal failure is occasionally followed by prolonged paralysis which necessitates continued mechanical ventilation (Riordan and Gilbertson, 1971; Abrams and Hornbein, 1975; Rouse, Galley and Bevan, 1977). In part, this is a consequence of the impaired renal excretion, decreased plasma clearance and prolonged duration of action of these drugs (McLeod, Watson and Rawlins, 1976; Miller et al., 1977; Somogyi, Shanks and Triggs, 1977). However, Miller and Cullen (1976) suggested that, in addition, in renal failure "recurarization" may follow the initital and apparently adequate antagonism of the neuromuscular blockade by neostigmine because the concentration of the neuromuscular blocker at the neuromuscular junction has not decreased sufficiently by the time the inhibition of acetylcholinesterase by neostigmine has terminated. However, as it has been demonstrated that the clearance of neostigmine is decreased also in patients with renal failure (Cronnelly et al., 1979), it seems unlikely that "recurarization", after apparently adequate antagonism of the blockade, would result from the relatively brief action of the antagonists. Nevertheless, prolonged studies of neuromuscular activity have not been reported following the antagonism of myoneural blockers with neostigmine in patients with renal failure.

In the present investigation pancuronium was administered to 20 patients with end-stage renal failure and neuromuscular transmission was monitored for 3 h after its attempted antagonism with neostigmine.

PATIENTS AND METHODS

Twenty patients with renal failure who were to undergo a variety of surgical procedures were studied. All had been dialysed within 72 h of surgery. Details of the patients, surgical procedures and laboratory data are shown in table I.

After the induction of anaesthesia with thiopentone 3–5 mg kg^{-1}, neuromuscular transmission was monitored using train-of-four stimulation according to the method of Ali, Utting and Gray (1970). The ulnar nerve was stimulated supramaximally at the elbow using subcutaneous needle electrodes. Trains-of-four square pulses of 0.2 ms duration at a frequency of 2 Hz and a train duration of 2 s were repeated every 10 s using a Grass S48 stimulator and SIU5 isolation unit. The hand and forearm were immobilized in a splint and the force of adduction of the adductor pollicis was measured with a force displacement transducer (Grass FT10) and recorded using a pen-and-ink recorder (Grass Polygraph).

After stabilization of the train-of-four recordings, suxamethonium 1 mg kg^{-1} was administered and the trachea intubated. Ventilation of the lungs was controlled using a

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TABLE I. *Patient data*

Patient No.	Sex	Age (yr)	Wt (kg)	Hb (g dl^{-1})	Na (mmol (litre^{-1})	K (mmol (litre^{-1})	Ca (mmol (litre^{-1})	Urea (mmol (litre^{-1})
Pancuronium 3 mg per 70 kg								
1	M	51	70	9.2	135	5.7	2.7	13.9
2	F	33	52	10.4	134	4.0	2.3	3.7
3	M	40	65	7.8	138	5.4	2.4	15.9
4	F	66	51	9.8	142	4.0	2.4	28.9
5	M	64	77	11.8	144	5.2	2.7	27.2
6	F	70	54	9.5	133	5.1	2.2	18.6
7	M	33	70	5.9	133	5.6	2.1	32.2
8	M	25	75	10.9	137	3.9	2.1	26.2
9	M	65	65	8.5	137	3.7	2.5	19.6
10	F	58	65	10.7	142	5.2	2.4	27.6
Mean		50.5	64.4	9.5	137.5	4.8	2.4	21.4
SEM		5.2	2.9	0.5	1.3	0.2	0.1	2.7
Pancuronium 6 mg per 70 kg								
1	M	57	67	8.2	144	4.2	2.6	22.9
2	M	23	63	7.1	138	5.5	2.9	38.8
3	F	36	85	9.1	136	4.7	2.3	18.9
4	F	27	56	6.2	143	4.7	2.6	25.9
5	F	24	55	9.9	139	4.7	2.7	29.9
6	M	27	68	6.7	140	3.9	2.5	20.6
7	F	43	55	8.1	142	3.3	2.3	17.9
8	F	19	50	7.7	143	4.5	2.3	16.6
9	M	24	70	7.1	138	3.2	2.8	19.6
10	F	21	40	7.1	140	4.5	2.3	12.9
Mean		30.1	60.9	7.7	140.3	4.3	2.5	22.4
SEM		3.8	4.0	0.4	0.8	0.2	0.1	2.4
P		<0.01	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.

partial rebreathing circuit and the minute volume was adjusted to maintain end-tidal carbon dioxide at 4–5%, assessed with a Beckman CO_2 analyser or according to a standard formula for fresh gas flow and minute ventilation (Bain and Spoerel, 1973). Anaesthesia was maintained with 70% nitrous oxide in oxygen with halothane (0.5–1% inspired). Pancuronium was administered, as soon as full recovery from suxamethonium was demonstrated, in a single dose of either 0.043 mg kg^{-1} (3 mg per 70 kg) or 0.086 mg kg^{-1} (6 mg per 70 kg) according to the anticipated duration of surgery. Ten patients were studied at each dose. When the height of the first twitch of each train, following the administration of pancuronium, returned to 10% of the control value, atropine 17 µg kg^{-1} (1.2 mg per 70 kg) and neostigmine 36 µg kg^{-1} (2.5 mg per 70 kg) were injected simultaneously. Controlled ventilation, assessment of neuromuscular transmission and anaesthesia were continued until the end of surgery, when the patient was transferred to the recovery room where neuromuscular monitoring was continued at 30-min intervals for at least 3 h after the administration of neostigmine. The train-of-four ratio (the height of the fourth twitch as a percentage of the first in each train) was used as the index of recovery of neuromuscular transmission.

The mean values are presented with the standard error of the mean as the index of dispersion. Probabilities were calculated from Student's t test for unpaired data where appropriate and the null hypothesis was rejected when $P<0.05$. Regression lines were constructed by the least squares regression method.

RESULTS

The two groups of patients were similar in their personal and biochemical characteristics except that the group which received the larger dose of pancuronium were significantly younger (table I).

In all patients, recovery of neuromuscular activity began within 2 min of receiving neostigmine and increased rapidly over the next 7–10 min to a quasi-plateau after which recovery

(Table I. *Patient data, continued*)

Patient No.	Creatinine (μmol litre^{-1})	Albumin (g litre^{-1})	Protein (g litre^{-1})	Operation
Pancuronium 3 mg per 70 kg				
1	804	32	63	Parathyroidectomy
2	327	35	63	Mastectomy
3	928	20	47	Transplant nephrectomy
4	371	33	66	A–V fistula
5	1582	39	65	Parathyroidectomy
6	751	36	74	Mastectomy
7	2007	29	54	A–V shunt
8	1211	28	49	A–V shunt
9	1123	44	70	A–V shunt
10	610	40	72	Incisional hernia
Mean	971	33.6	62.3	
SEM	167	2.2	3.0	
Pancuronium 6 mg per 70 kg				
1	1344	38	58	Parathyroidectomy
2	1450	36	65	Bilateral nephrectomy
3	964	38	68	Renal transplant
4	955	34	60	Parathyroidectomy
5	1132	40	66	Renal transplant
6	946	49	69	Renal transplant
7	672	36	57	Renal transplant
8	893	34	50	A–V shunt
9	1025	41	59	Renal transplant
10	356	40	59	Renal transplant
Mean	974	38.6	55.9	
SEM	98	1.4	5.9	
P	n.s.	n.s.	n.s.	

Table II. *Time (min) to 10% spontaneous recovery and train-of-four (%) after neostigmine*

	Time to 10% recovery (min)	Time after neostigmine (min)											
		1	2	3	4	5	10	30	60	90	120	150	180
Pancuronium 3 mg per 70 kg													
Mean	26.6	6.8	21.6	31.9	40.0	46.3	64.7	80.2	86.6	91.2	93.4	94.6	96.9
SEM	±6.4	2.8	4.8	4.9	5.0	5.3	4.6	3.6	3.2	2.4	1.6	1.6	1.5
Pancuronium 6 mg per 70 kg													
Mean	102.1	—	7.6	16.4	24.7	31.9	53.0	60.9	70.3	77.3	84.0	87.4	89.3
SEM	±14.7	—	1.6	2.4	3.2	4.3	5.1	5.4	3.3	4.3	4.9	4.7	4.5
P	<0.01	—	<0.05	<0.05	<0.05	<0.05	n.s.	<0.05	<0.05	<0.05	n.s.	n.s.	n.s.

progressed more slowly. Recovery was progressive in every patient: there was no evidence of deterioration of neuromuscular transmission in any patient during the period of study. The rate of recovery was more rapid in the group that had received the smaller dose of pancuronium (fig. 1; table II) and the difference was significant for up to 90 min after antagonism. In addition, there was a negative correlation between the duration of the neuromuscular block (time from injection to 10% spontaneous recovery) and the degree of recovery at timed intervals after antagonism (fig. 2).

The mean train-of-four ratios in the two groups exceeded 70% at 60 min and were nearly 90% at 180 min after neostigmine. Nevertheless, two

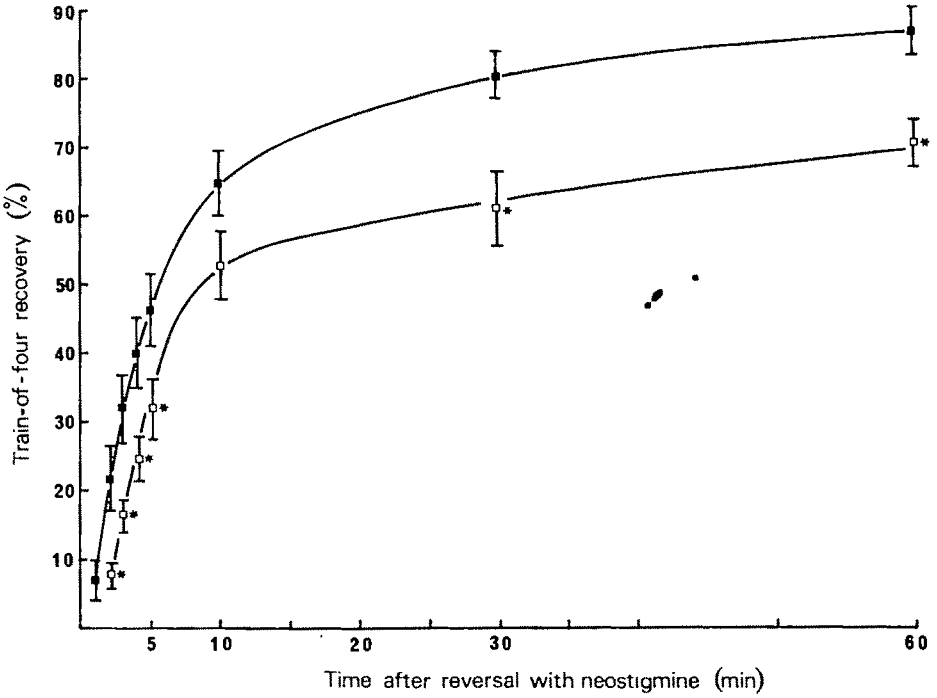

FIG. 1. Train-of-four recovery (%) after antagonism of pancuronium 3 mg (■) or 6 mg (□) per 70 kg, with neostigmine, 2.5 mg per 70 kg.

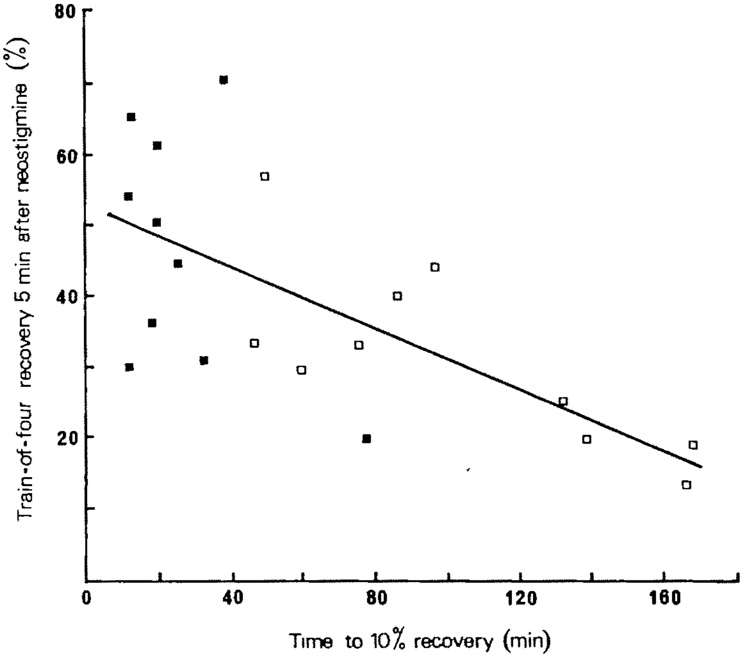

FIG. 2. Relationship between duration of paralysis (time to 10% spontaneous recovery of neuromuscular activity) and train-of-four recovery 5 min after antagonism of pancuronium 3 mg (■) or 6 mg (□) per 70 kg with neostigmine.

patients in the high-dose pancuronium group had delayed recovery: at 1 h, train-of-four ratios were 50 and 52% and in the first this had only recovered to 54% at 3 h. Additional neostigmine at this time produced rapid recovery to 70% train-of-four.

DISCUSSION

These results confirm that the antagonism of non-depolarizing neuromuscular blocking drugs in patients with renal failure is followed by progressive recovery of neuromuscular transmission and that "recurarization" as a result of the brief action of the anticholinesterase is unlikely.

Pharmacokinetic studies have demonstrated delayed excretion of all the commonly-used non-depolarizing myoneural blockers in renal failure (Feldman, Cohen and Golling, 1969; Miller et al., 1977; Duvaldestin et al., 1979). In particular, the plasma clearance of pancuronium is decreased by 50–75% (McLeod, Watson and Rawlings, 1976; Somogyi, Shanks and Triggs, 1977). The delayed plasma clearance is associated with a slow decrease in the concentration of the drugs at the neuromuscular junction and, therefore, slow spontaneous recovery of neuromuscular activity. Antagonism of the non-depolarizing myoneural blockers with anticholinesterases can be considered as an acceleration in the rate of spontaneous recovery. Thus, the antagonists will appear to be less effective in situations where spontaneous recovery is greatly impaired, for example in renal failure. This is further confirmed in the present study, by the negative correlation between the duration of action of pancuronium and the degree of recovery 5 min after neostigmine (fig. 2). Similarly, the significantly impaired rate of recovery using larger doses of pancuronium confirms the prediction that renal failure primarily affects the duration of action and, therefore, the rate of recovery of large single doses or multiple doses of non-depolarizing drugs (Gibaldi, Levy and Hayton, 1972).

Recurarization may not have been observed in these patients because the clearance of neostigmine is also impaired in renal failure (Cronnelly et al., 1979). However, it may not be necessary for anticholinesterases to exert a prolonged action to achieve progressive recovery of neuromuscular function. Recurarization implies that the displaced myoneural blocker re-occupies the receptor after the action of neostigmine has terminated. If neostigmine is administered when spontaneous recovery is occurring, the plasma concentration of the blocking drug is probably too low for any re-occupation sufficient to intensify paralysis to occur.

Although this study has demonstrated the improbability of recurarization after reversal of neuromuscular blockade in renal failure, it has also shown that when large doses of these drugs are used their antagonism may occasionally be slow and unpredictable. In such situations administration of narcotics for the relief of pain may result in respiratory depression and hypercapnia and may potentiate the residual effect of the myoneural blocking drug (Katz and Wolf, 1964) or prevent its complete antagonism by neostigmine (Miller and Roderick, 1978). This sequence might explain the reports of recurarization following initially adequate reversal of non-depolarizing drugs. Consequently, patients in renal failure require careful monitoring of neuromuscular activity, additional neostigmine if indicated and judicious use of respiratory depressant drugs following operation.

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ANTAGONISME DU PANCURONIUM DANS LES CAS D'INSUFFISANCE RENALE: AUCUNE RECURARISATION

RESUME

On a mesuré à l'aide de stimulations par chaînes de quatre la transmission neuromusculaire, pendant et après l'anesthésie, sur 20 patients souffrant d'une insuffisance rénale au stade terminal. Le blocage neuromusculaire a été assuré à l'aide de pancuronium administré en doses uniques de 3 ou de 6 mg par 70 kg et on l'a antagonisé à 10% de la récupération à l'aide d'atropine et de néostigmine administrées à raison de 2,5 mg par 70 kg. Cette inversion a été suivie d'une récupération progressive de la contraction musculaire sur chaque patient pendant les 3 h nécessaire à l'etude. La récupération a été plus rapide après les plus faibles doses de pancuronium, et elle a été inversement corrélée à durée du blocage. Il en a été conclu que lorsque le pancuronium est antagonisé à l'aide de néostigmine sur des patients souffrant d'une insuffisance rénale, la transmission neuromusculaire reprend sans qu'il y ait une indication de recurarisation. Cependant, lorsque les fortes doses de pancuronium sont antagonisées à l'aide de 2,5 mg de néostigmine, la récupération peut être insuffisante pour assurer une fonction ventilatoire normale.

BEKÄMPFUNG VON PANCURONIUM BEI NIERENVERSAGEN—OHNE REKURARISIERUNG

ZUSAMMENFASSUNG

Die neuromuskuläre Übertragung vor und nach der Anästhesie wurde mittels Vierezug Reizung bei 20 Patienten mit Endstadium-Nierenversagen gemessen. Die neuromuskuläre Blockade wurde mittels Pancuronium in einzelnen Dosen von entweder 3 oder 6 mg pro 70 kg hergestellt und bei 10% Erholung mittels Atropin und Neostigmin 2,5 mg pro 70 kg bekämpft. Nach der Umkehr stellte sich eine progressive Erholung der Muskelzuckung bei jedem Patient während der 3-stündigen Untersuchung ein. Die Erholung ging nach der kleineren Dosis schneller vor sich und es bestand eine inverse Korrelation zu der Dauer der Blockade. Es wird der Schluss gezogen, dass wenn Pancuronium bei Patienten mit Nierenversagen mit Neostigmin bekämpft wird, die neuromuskuläre Übertragung sich ohne Anzeichen einer Rekurarisierung erholt. Wenn grössere Dosen von Pancuronium mit Neostigmin 2,5 mg bekämpft werden, kann es vorkommen, dass die Erholung nicht ausreicht, um die normale Ventilationsfunktion zu gewährleisten.

CONTRARRESTO DEL PANCURONIO EN EL FALLO RENAL: NINGÚN RECURARIZACIÓN

SUMARIO

Se midió la transmisión neuromuscular mediante simulación del tren-de-cuatro impulsos, durante la anestesia, y después de ésta, de 20 pacientes en la última fase de fallo renal. El bloqueo neuromuscular se proveyó mediante pancuronio, en dosis únicas de 3 mg ó de 6 mg por cada 70 kg, y se contrarrestó, hasta una recuperación del 10%, mediante atropina y neostigmina en cantidades de 2,5 mg por cada 70 kg. Al proceso inverso le siguió la recuperación progresiva y espasmódica del tejido muscular en cada uno de los pacientes, durante las tres horas del estudio. La recuperación fue más rápida a raíz de la administración de dosis más pequeñas de pancuronio y presentó una correlación inversa en relación a la duración del bloqueo. La conclusión es que cuando el pancuronio se contrarresta con la neostigmina en pacientes con fallo renal, la transmisión neuromuscular se recupera sin evidencia alguna de recurarización. No obstante, cuando se contrarrestan grandes cantidades de pancuronio con 2,5 mg de neostigmina, la recuperación puede que sea insuficiente para garantizar una función ventiladora normal.

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SPINAL ANALGESIA WITH HYPERBARIC BUPIVACAINE: EFFECTS OF VOLUME OF SOLUTION

K. O. SUNDNES, P. VAAGENES, P. SKRETTING, B. LIND AND H. H. EDSTRÖM

SUMMARY

The effects of 0.5% bupivacaine 1.5, 2 and 3 ml in 8% glucose were compared in a double-blind study involving 30 patients undergoing spinal analgesia. The time to the onset of maximum segmental spread of analgesia was approximately 15 min for all three volumes. Cephalad spread of analgesia was related to the volume used: 1.5 ml reached T10, 2 ml T8 and 3 ml T7. The duration of analgesia increased with increasing volume, 3 ml producing analgesia in T8–T12 for 1.5–2 h, and in the lumbar region for 2.5–3 h. Increasing the volume increased the extent of motor blockade and speeded up its onset. Significant decreases in arterial pressure were observed in the 2- and 3-ml groups. The changes in heart rate were moderate and not correlated with the amount of drug. Spinal headache occurred in two patients.

Previous studies (Hengesbach and Matthes, 1977; Nolte et al., 1977) have described the use of bupivacaine solution without glucose in the production of spinal analgesia. However, since the addition of glucose alters the anaesthetic profile of intrathecal solutions (Brown et al., 1980; Chambers, Edström and Scott, 1981), this study was undertaken to compare the efficacy of three different volumes of 0.5% bupivacaine in 8% glucose administered for spinal analgesia during urological operations.

PATIENTS AND METHODS

Twenty-nine men and one woman undergoing urological surgery with spinal analgesia were randomly allocated to receive 0.5% bupivacaine 1.5, 2 or 3 ml in 8% glucose. Information about the study was given to each patient and consent obtained according to the Helsinki declaration.

Premedication (diazepam according to age and weight) was given by mouth 45–60 min before the induction of anaesthesia. Immediately before the institution of the spinal blockade, 200–300 ml of lactated Ringer's solution was infused i.v. Lumbar puncture was performed with a 22-gauge spinal needle using a midline approach with the patient in the lateral recumbent position. The second or third lumbar interspace was chosen for the puncture and, when a free flow of clear cerebrospinal fluid was obtained, the local anaesthetic solution was injected at the rate of 0.2–0.25 ml s^{-1} without barbotage. Immediately after the injection the patient was positioned in the supine horizontal position, and 15–20 min thereafter in the lithotomy position.

The cephalad spread of analgesia (loss of sensation to pinprick) was determined with a short-bevelled needle every 2 min for 30 min after the induction of the block.

Motor block was assessed according to the following scale by recording the degree of motor function of the lower extremities following each determination of analgesia (Bromage, 1965): 0 = no paralysis (full flexion of knees and feet); 1 = inability to raise the extended leg (just able to move knees); 2 = inability to flex knees (able to move feet only); 3 = inability to flex the ankle joint (unable to move feet or knees).

Thereafter analgesia and motor block were assessed every 15 min until analgesia had totally disappeared or for a maximum of 5 h after injection.

Heart rate and arterial pressure (sphygmomanometry) were recorded before and 2, 5, 10, 15, 20 and 30 min after the injection and thereafter every 30 min until normal sensation had returned (maximum 3 h after injection).

The patients were observed for 48 h for possible signs of post-spinal complications.

The differences between means were analysed with Student's *t* test and differences between frequencies by the Fischer exact test.

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TABLE I. *Summary of the clinical data for the three groups; mean values between block and start of operation (inj.–op.) and duration of surgical procedure (mean ± SEM)*

Volume	Age (yr)	Weight (kg)	Height (cm)	Interval inj.–op. (min)	Duration of op. (min)
1.5 ml (n = 10)	68.9 ± 1.63	68.6 ± 2.99	174 ± 1.87	31.8 ± 4.35	36.4 ± 3.72
2.0 ml (n = 10)	68.2 ± 1.84	76.8 ± 4.68	174 ± 2.55	35.1 ± 5.92	30.3 ± 7.68
3.0 ml (n = 10)	68.1 ± 2.07	76.7 ± 1.37	177 ± 2.78	28.5 ± 3.26	46.1 ± 5.35

RESULTS

There were no statistical differences between the three groups in relation to characteristics of the patients or the duration of the operations (table I).

Sensory spread

Maximum spread of analgesia appeared 11–20 min after injection, and the onset was similar for each volume (fig. 1; table II). The spread to the S3–S5 dermatomes was rapid (within 2 min in 18 patients and within 4 min in 27 patients) regardless of the volume used. In two patients, both in the 1.5-ml group, caudal spread was unsatisfactory.

In one patient analgesia at the L5 dermatome was delayed for 22 min, while the L4 and S1 dermatomes were blocked within 4–5 min.

The mean maximum spread of analgesia tended to increase with increasing volume, from T10 with 1.5 ml to T7 with 3 ml, the differences between 1.5 and 2 ml and between 1.5 and 3 ml being significant ($P < 0.05$) (fig. 1).

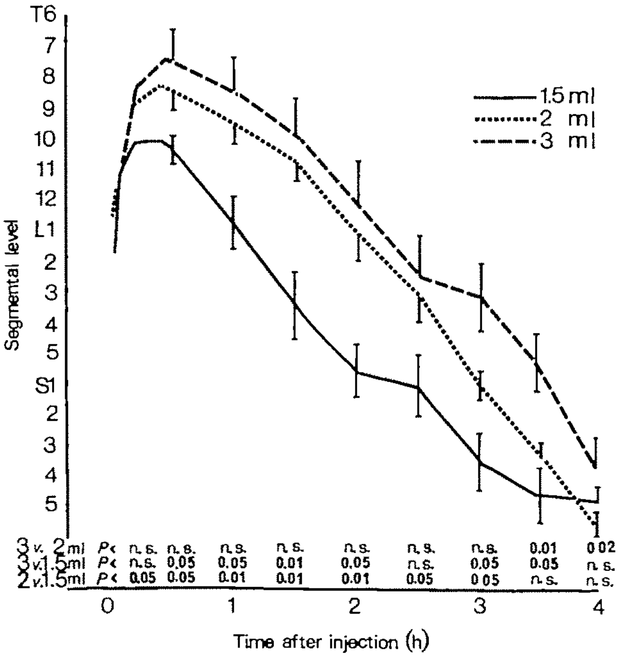

FIG. 1. Segmental spread of analgesia for different volumes (ml) of bupivacaine (mean ± SEM). P-values show differences between the groups at different time intervals.

TABLE II. *Maximum upper segmental level of analgesia and time to attain this for each volume (dependant side). Mean ± SEM*

Volume	Thoracic level	Time (min)
1.5 ml ($n = 10$)	10.1 ± 0.48	11.8 ± 6.48
2.0 ml ($n = 10$)	8.3 ± 0.70	14.4 ± 1.63
3.0 ml ($n = 10$)	7.6 ± 1.08	15.7 ± 2.31

There was no correlation between the site of injection, the maximum cephalad spread of analgesia and the time to reach this level.

In 13 patients analgesia reached a higher maximum upper level on the dependant compared with the non-dependant side. The difference was usually only one, occasionally two segments (except in patient No. 9: five segments), and this feature was distributed equally among the groups, although it was more pronounced in the 1.5-ml group (fig. 2). In 15 patients there was no difference between the two sides and in two patients the highest level was reached on the non-dependant side.

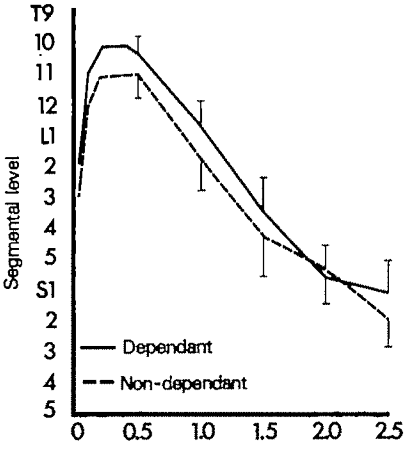

FIG. 2. Segmental spread of analgesia on the dependant and non-dependant sides with 1.5 ml of bupivacaine (mean ± SEM).

Motor blockade

The time of onset for different degrees of motor blockade did not differ significantly between the three volumes. Six patients in the 3-ml group, four patients in the 2-ml and one in the 1.5-ml group, had complete motor blockade (degree 3) of both lower extremities (table III). The difference in frequency between 1.5 ml and 3 ml was significant ($P < 0.05$).

TABLE III. *Frequency of total motor blockade and time for complete recovery (mean ± SEM) for each volume (dependant side)*

Volume	Duration (min)	No.
1.5	84.6 ± 9.18	3
2.0	128.0 ± 9.92	6
3.0	162.0 ± 19.00	8

Duration

Figure 1 shows that the duration of analgesia at different segmental levels increased with increasing volume of the local anaesthetic solution. Significant differences in duration at different levels were found between the smaller volume (1.5 ml) and the larger volumes (2 and 3 ml). No significant difference was found between 2 ml and 3 ml, nor was there any significant difference in the duration of analgesia on the dependant and non-dependant sides.

In 20 of 25 patients the S5 dermatome was the last dermatome in which normal sensation was restored. In six patients (five in the 3-ml and one in the 2-ml group) analgesia lasted for longer than the period of assessment (5 h) in both the S3 and the S5 dermatomes. In six patients (2 ml: four, 3 ml: one, 1.5 ml: one) regression was faster in the L5–S1 dermatomes on the non-dependant side and this is illustrated in one patient in figure 3. In one patient this occurred exclusively on the dependant side and, in another, more rapid regression was observed in the L5–S1 dermatones bilaterally.

The duration of motor blockade of different degrees increased with increasing volume. In the 3-ml group complete paralysis of both lower extremities occurred in six of 10 patients with a mean duration of 127 ± 50 min.

After the return of normal sensation residual motor blockade did not occur. Significant differences in duration were found between 1.5 ml and 2 ml, and between 1.5 ml and 3 ml.

Adequacy of analgesia

For transurethral resection 2–3 ml of the solution was required to produce adequate analgesia. Systemic analgesics were needed in three patients and additional sedation in two.

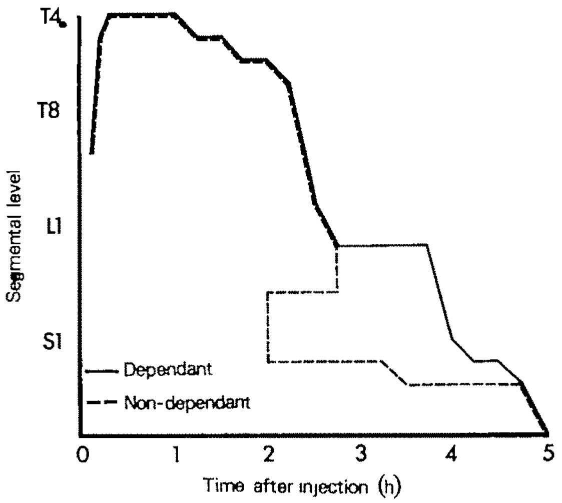

FIG. 3. Segmental spread of analgesia illustrating faster regression the L5/S1 dermatomes on the non-dependant side in patient No. 13 (3 ml of bupivacaine).

Arterial pressure and heart rate

Arterial pressure did not differ significantly between the groups before blockade. After injection arterial pressure decreased from 131±5 mm Hg to 119±5 mm Hg ($P<0.1$), from 128±5 mm Hg to 107±3 mm Hg ($P<0.0025$), and from 131±6 mm Hg to 107±5 mm Hg ($P<0.005$) in the 1.5-, 2- and 3-ml groups respectively. Eight patients (four in the 3-ml group, three in the 2-ml group, and one in the 1.5-ml group) received ephedrine after institution of the blockade because of a decrease in arterial pressure to 100 mm Hg or less. Atropine was administered to one patient because of a concomitant decrease in heart rate and arterial pressure. All of those patients who required ephedrine or atropine had a cephalad spread of analgesia up to, or above, T9.

Changes in heart rate varied from +10.6% to −8.8%. Twelve patients (equally distributed among the groups) had an initial and persistent decrease in heart rate, while in seven patients an initial increase was rapidly followed by a persistent decrease.

Complications

Post-spinal headache was encountered in two patients (6.8%) and two patients complained of backache at the site of injection. Another two patients complained of headache which was not attributed to the spinal anaesthesia.

DISCUSSION

In the present study 2 ml and 3 ml of hyperbaric 0.5% bupivacaine administered intrathecally with the patient in the horizontal position, gave adequate analgesia for transurethral surgery in 18 of 20 patients. In the 1.5-ml group two patients expressed apprehension, and two patients felt pain although systemic analgesics were given to one only. Cephalad spread of analgesia was generally less for these patients compared with the group as a whole. In the patient who received systemic analgesics it was observed that caudal spread of the analgesia was unsatisfactory. One patient in each of the two other groups received supplementary analgesics, and it was particularly noticeable that the maximum cephalad spread in these two was much less (T12 and L1) than average for the groups (table II). The inadequate analgesia in these two patients was assumed to be a result of faulty positioning of the needle, with the bevel situated partly extradurally or in the potential subdural space. This problem is given special mention in textbooks of radiology (Shanta and Evans, 1972; Sutton and Grainger, 1975), and may be eliminated by barbotage.

The main factors determining the effect of agents used in spinal anaesthesia are the amount of drug given, the total volume of the solution, its density, positioning of the patient, speed of injection, barbotage, and the use of vasoconstrictors (Bonica, 1967; Lund, 1971; Covino and Vassallo, 1976; Nolte and Stark, 1979). To some extent pH of the solution, added preservants and the tolerance to autoclaving and storage may alter the pharmacological characteristics of the drug (Stark, Gergs and Nolte, 1977; Dudziak and Uihlein, 1978; Stark and Nolte, 1978; information from ASTRA Chemical Group).

In the present study the time of onset of maximum segmental spread of analgesia was similar with each volume (fig. 1) while the degree of spread and the duration of analgesia varied with the volume administered (fig. 1).

In spite of turning the patient immediately into the supine horizontal position, there was a tendency for a higher cephalad spread, and a prolonged effect on the dependant side (fig. 2). Although a similar effect was observed by Wildsmith and colleagues (1981), usually the spread is similar on both sides, and no significant differences can be established.

It was apparent that increasing the dosage from 2 to 3 ml did not increase spread and duration to the same extent as the increase from 1.5 to 2 ml (up to 2.5–3 h).

There were no differences in the spread of analgesia between injections made at the L2/3 or the L3/4 levels. However, the number of patients was small and the choice of puncture site was not randomized.

Contrary to previous reports on regression of analgesia (Nolte and Stark, 1979) we found a more persistent effect in the lowest dermatomes (S2/S5). This may be of practical value in surgical procedures of the urethra and the anal regions.

Failure to achieve satisfactory analgesia at the L5 and S1 dermatomes has been associated with extradural blockade (Knoche, Traub and Dick, 1979). We observed the same problem in nine patients although, to our knowledge, this has not been reported with spinal analgesia. The complication can be explained by postulating a common site of action for both central neural blocks, but the underlying mechanism is not clear.

Motor blockade was satisfactory for transurethral resection in all groups. However, the frequency of complete blockade was low, even in the 3-ml group (six of 10). This must be considered when this method is used and full muscular relaxation is desired. The changes in arterial pressure and heart rate were considered to be moderate although eight patients received ephedrine. A decrease in arterial pressure was often related to a concomitant slowing of the heart rate. This has been observed with intrathoracic intercostal nerve blockade and may be related to a secondary sympathiolytic effect on the heart (Skretting, 1981).

With a 22-gauge needle post-spinal headache was observed in only 6.8% of patients. This low frequency is probably related to the relatively high mean age of our patients. In other reports of younger patient groups a frequency of post-spinal headache of up to 20% has been registered although needles of finer bore have been used (Chambers, Edström and Scott, 1981).

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ANESTHESIE RACHIDIENNE A L'AIDE DE BUPIVACAINE HYPERBARE: EFFETS DU VOLUME DE LA SOLUTION

RESUME

Nous avons comparé au cours d'une étude à double insu les effets de la bupivacaïne à 0,5% administrée à raison de 1,5 2 et 3 ml dans 8% de glucose, cela mettant en cause 30 patients devant subir une anesthésie rachidienne. Le temps nécessaire au départ de la propagation segmentaire maximale de l'anesthésie a été d'environ 15 min pour les trois volumes. La propagation de l'anesthésie en direction de la tête a été liée au volume utilisé: 1,5 ml a atteint T10, 2 ml T8 et 3 ml T7. La durée de l'analgésie a augmenté en fonction de l'augmentation du volume, 3 ml produisant une analgésie dans la région

T8–T12 pendant 1,5–2 h et dans la région lombaire pendant 2,5–3 h. L'accroissement du volume a entraîné une augmentation du blocage moteur et accéléré son déclenchement. Nous avons observé dans les groupes 2 ml et 3 ml des diminutions importantes de la pression artérielle. Les variations dans la fréquence cardiaque ont été modérées et n'ont pas subi d'influence liée à la quantité d'agent anesthésiant. Deux patients se sont plaints de céphalée spinale.

LUMBALANALGESIE MIT HYPERBAREM BUPIVACIN: AUSWIRKUNGEN DES LÖSUNGSVOLUMENS

ZUSAMMENFASSUNG

Die Auswirkungen von 1, 5, 2 und 3 ml 0,5% Bupivacain in 8% Glukose wurden während einer Doppelblinduntersuchung bei 30 Patienten verglichen, die sich einer Lumbalanalgesie unterzogen. Die Zeit bis zum Einsetzen der maximalen Segmentalverteilung der Analgesie betrug bei jedem der drei Volumen ca. 15 Minuten. Es ergab sich dabei eine Beziehung zwischen der Verbreitung der Analgesie in Kopfrichtung und dem angewandten Volumen: bei 1,5 ml wurde T10 erreicht, bei 2 ml T8 und bei 3 ml T7. Die Dauer der Analgesie stieg mit steigendem Volumen an. Bei 3 ml erreichte die Analgesie T8–T12 auf die Dauer von 1,5 bis 2 Stunden, und 2,5 bis 3 Stunden in der Lendengegend. Eine Steigerung des Volumens führte zu einer Ausbreitung der motorischen Blockade und zu einem schnelleren Einsetzen derselben. Bedeutende Abnahmen des Arteriendruckes wurden bei den 2-ml und 3-ml Gruppen beobachtet. Die Änderungen im Herzschlag waren mässig und es bestand dabei keine Korrelation zu dem Drogenvolumen. Spinale Kopfschmerzen stellten sich bei zwei Patienten ein.

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ANALGESIA DE LA ESPINA DORSAL MEDIANTE BUPIVACAINA HIPERBARICA: EFECTOS DE LA SOLUCION EN FUNCION DEL VOLUMEN

SUMARIO

Se compararon los efectos de 1,5, 2 y 3 ml de bupivacaína al 5%, en glucosa al 8%, en un estudio de doble anonimato efectuado en 30 pacientes sometidos a analgesia de la espina dorsal. El tiempo transcurrido hasta el comienzo de la máxima dispersión segmental fue de aproximadamente 15 minutos para los tres volúmenes. La dispersión cefálica de la analgesia estuvo en función del volumen usado: 1,5 ml alcanzaron T10, 2 ml alcanzaron T8 y 3 ml alcanzaron T7. La duración de la analgesia aumentó al aumentar el volumen, produciendo el volumen de 3 ml una analgesia de T8–T12 por espacio de 1,5 a 2 horas, y en la región lumbar por espacio de 2,5 a 3 horas. El incremento del volumen incrementó el alcance del bloqueo motriz y aceleró su comienzo. Se observaron disminuciones significativas en la presión arterial en los grupos de 2 y de 3 ml. Los cambios del ritmo cardiaco fueron moderados y sin correlación con la cantidad de droga. Dos de los pacientes sufrieron dolores en la espina dorsal.

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SPINAL ANAESTHESIA WITH HYPERBARIC BUPIVACAINE: EFFECTS OF CONCENTRATION AND VOLUME ADMINISTERED

W. A. CHAMBERS, D. G. LITTLEWOOD, H. H. EDSTROM AND D. B. SCOTT

SUMMARY

A double-blind study was carried out using hyperbaric solutions of bupivacaine to compare the effects of varying the concentration of bupivacaine and the volume of solution administered intrathecally. Fifty-seven patients were studied. Ten patients received each volume of each concentration: 0.5% bupivacaine in 8% dextrose, 2 ml, 3 ml or 4 ml and 0.75% bupivacaine in 8% dextrose, 1.3 ml or 2 ml. A further seven patients received 3 ml of the 0.75% solution. Both solutions consistently produced good nerve blockade. With the 0.5% solution, increases in the volume administered had no effect on the spread of sensory loss, whereas with the 0.75% solution, increasing the volume administered resulted in a significantly greater cephalad spread. The use of 3 ml of this solution was abandoned after seven patients had received it because of the excessive spread. With both solutions, increasing the volume produced a longer duration of action. The use of a 0.75% solution of hyperbaric bupivacaine for spinal anaesthesia did not appear to confer any advantage over the 0.5% solution.

Bupivacaine hydrochloride 0.5% and 0.75% have been used fairly extensively to produce spinal anaesthesia (Nolte et al., 1977; Lanz, Schellenberg and Theiss, 1979; Nolte and Stark, 1979). However, relatively little is known about the behaviour of this agent when administered in hyperbaric solution. In a previous study we compared the effects of the subarachnoid administration of 0.5% bupivacaine 3 ml in 0%, 5% and 8% dextrose and found that 0.5% bupivacaine in 8% dextrose was suitable for spinal anaesthesia (Chambers, Edstrom and Scott, 1981). Since 0.75% bupivacaine offers certain advantages compared with 0.5% bupivacaine when these solutions are administered extradurally (Scott et al., 1980), the present study was undertaken to compare the effects of different volumes of 0.5% bupivacaine in 8% dextrose and 0.75% bupivacaine in 8% dextrose following intrathecal injection.

PATIENTS AND METHODS

Fifty-seven patients about to undergo transurethral resection of the prostate, or lower limb or perineal surgery under spinal anaesthesia took part in the study. All gave informed consent for the investigation which was approved by the hospital ethical committee. About 1 h after premedication with diazepam 10 mg by mouth an i.v. infusion was established. A lumbar puncture was performed using a 22-gauge needle with the patient lying on his right side on a horizontal table. After a free flow of cerebrospinal fluid was obtained, the test solution was injected without barbotage at a rate of 1 ml every 5 s. Two millilitre, 3 ml or 4 ml of the 0.5% solution and 1.3 ml or 2 ml of the 0.75% solution was injected such that 10 patients received each volume of each concentration. A further seven patients received 3 ml of the 0.75% solution. Originally, it was intended to give 3 ml of the 0.75% solution to 10 patients, but for reasons given below this part of the study was abandoned after seven patients. However, these seven patients were included in the randomization of all the other groups of patients. The solution injected in each instance was determined from a random list and was known only to the anaesthetist performing the block. Immediately after injection the needle was withdrawn and the patient turned supine.

Assessments of the sensory and motor blockade, and measurements of arterial pressure and heart rate were obtained at 2, 5, 8, 10, 15, 20, 25 and 30 min after injection by another anaesthetist (W.A.C.) who had not been present during the injection and was unaware of the nature of the solution used. Sensory loss was assessed using a short-bevelled 22-gauge needle, and was tested in the anterior axillary line on the trunk, on the legs

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and perineum, and when necessary on the arms. Analgesia was defined as loss of the sensation of pinprick and anaesthesia as loss of the sensation of touch. Motor block in the legs was assessed on a 0–3 scale: 0 = full movement of leg; 1 = inability to raise extended leg; 2 = inability to flex the knee; 3 = inability to flex the ankle. During the 30-min period of assessment, Hartmann's solution 500 ml was infused i.v.

After 30 min the patient was positioned for surgery. A note was made of the operating conditions and the need for any additional medication.

Following, and when possible during, surgery, further assessments of the sensory and motor loss were made at 15-min intervals until there was no demonstrable sensory loss.

The results were analysed using the Student t test, Fisher's exact test and Wilcoxon's rank test, $P < 0.05$ being taken to indicate a significant difference.

RESULTS

There were no significant differences between the mean ages, weights or heights of the patients in each of the six groups (table I).

TABLE I. *Mean (± SEM) age, weight and height of patients in each group*

Solution used	Age (yr)	Weight (kg)	Height (cm)
0.5% 2 ml	63.7±5.9	72.6±3.9	172±2.3
0.5% 3 ml	64.1±4.3	67.1±4.0	172±2.6
0.5% 4 ml	60.4±4.5	75.2±5.1	173±2.3
0.75% 1.3 ml	69.5±2.5	68.5±2.0	168±2.4
0.75% 2 ml	63.5±3.2	80.0±4.4	174±1.7
0.75% 3 ml	67.7±6.8	72.2±3.7	169±4.5

Sensory loss

The mean upper segmental levels of analgesia in each group at times up to 30 min are shown in figures 1 and 2. Varying the volume of the 0.5% solution did not produce any significant differences in the spread of analgesia at any of the times up to 30 min. In contrast, with the 0.75% solution there was a clear tendency for increased spread with an increase in volume and the differences between 1.3 ml and 2 ml and between 1.3 ml and 3 ml were significant.

The spread of anaesthesia was, on average, three segments less than that of analgesia and analysis showed the same differences between groups as that for analgesia.

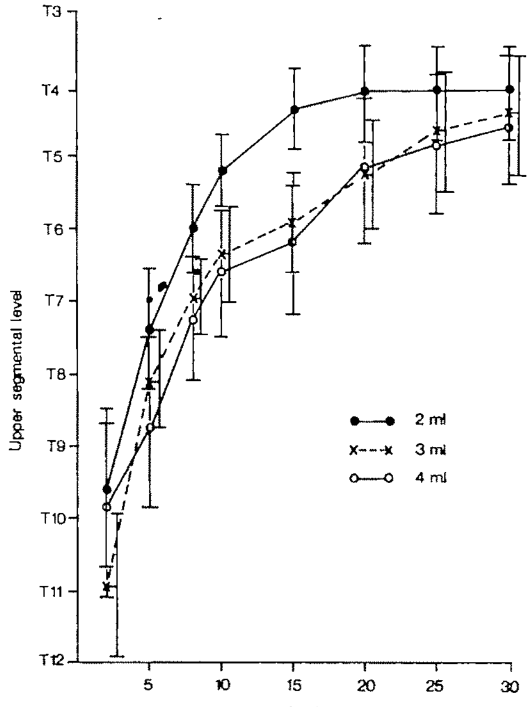

FIG. 1. Mean cephalad spread (± SEM) of analgesia at times up to 30 min in three groups of patients who received different volumes of 0.5% bupivacaine in 8% dextrose.

TABLE II. *Mean (± SEM) time (min) until spread of sensory loss was maximal in each group of patients*

Solution used	Mean time (± SEM) to max. spread (min)
0.5% 2 ml	14.7±1.9
0.5% 3 ml	20.8±2.2
0.5% 4 ml	19.6±3.1
0.75% 1.3 ml	11.7±2.0
0.75% 2 ml	20.5±2.2
0.75% 3 ml	20.0±2.3

The mean time in each group until the spread of sensory loss was complete is shown in table II and was significantly shorter using 1.3 ml of the 0.75% solution compared with any of the others.

Motor block

Motor block in the legs was complete in eight of the 10 patients who received 1.3 ml of the 0.75% solution, in all seven of the patients who received 3 ml of the 0.75% solution and in nine of the 10 patients in each of the other groups (table III). There was no significant difference in the frequency of degrees of motor block between the

TABLE III. *Number of patients in each group who achieved each degree of motor block in the legs and the mean (±SEM) time (min) in each group taken to achieve it*

	Degree of motor block					
	1		2		3	
Solution used	No. of patients	Time (min)	No. of patients	Time (min)	No. of patients	Time (min)
0.5% 2 ml	10	2.6±0.9	8	2.7±0.5	8	6.4±2.1
0.5% 3 ml	10	4.4±1.9	9	4.0±1.4	9	6.2±1.7
0.5% 4 ml	10	3.1±1.4	9	4.8±1.9	9	6.3±2.0
0.75% 1.3 ml	10	3.2±0.7	10	6.2±1.7	9	7.0±1.2
0.75% 2 ml	10	4.4±1.8	9	4.9±0.5	9	8.2±1.2
0.75% 3 ml	7	2.0±0	7	2.6±0.2	7	7.9±1.2

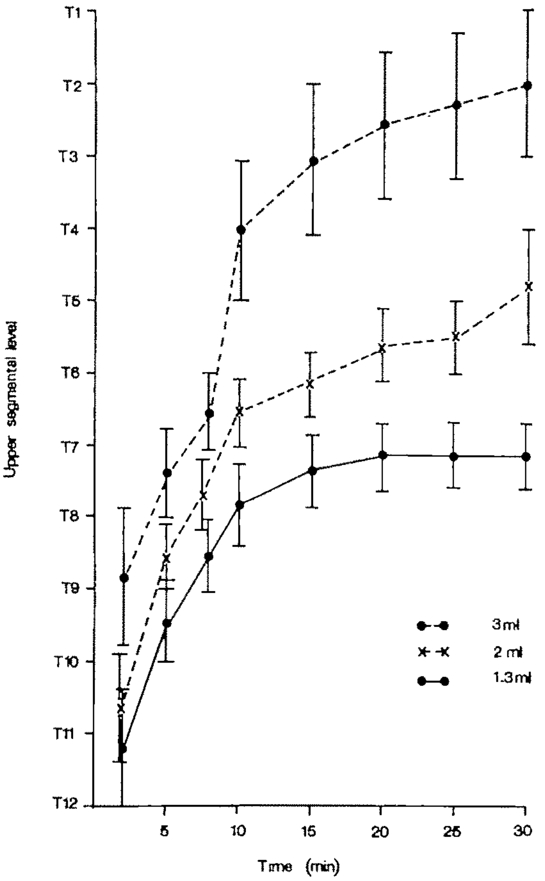

FIG. 2. Mean cephalad spread (±SEM) of analgesia at times up to 30 min in three groups of patients who received different volumes of 0.75% bupivacaine in 8% dextrose.

groups. The mean times to reach different degrees of motor block are shown in table III. There were no significant differences with regard to the time of onset with the 0.5% solution. With the 0.75% solution, 3 ml produced a significantly more rapid onset to degree 1 than 1.3 ml and a significantly more rapid onset to degree 2 than 2 ml or 1.3 ml.

Cardiovascular changes

Systolic arterial pressure decreased by an average of 20–25% in each of the groups. Four patients (two of whom had received 3 ml of the 0.75% solution) received ephedrine because of a severe decrease in arterial pressure and a further two patients received atropine on account of bradycardia. One patient who had received 3 ml of the 0.75% solution died 90 min after injection. He had no significant past medical history and the only evidence of ischaemic heart disease before surgery was minor changes on his electrocardiogram. His arterial pressure was 120/80 mm Hg before surgery. After injection he developed analgesia to T1 and his arterial pressure decreased to 90/60 mm Hg. He remained asymptomatic and 35 min after injection, surgery commenced. Sixty minutes after injection the patient complained of pain and tightness in his neck and jaw. He looked ashen and was sweating. He was treated with sublingual glycerol trinitrate with no effect. His arterial pressure decreased and, despite intubation of the trachea, 100% oxygen and treatment with various vasopressors he suffered a cardiac arrest from which he could not be resuscitated, After this incident, an independent observer analysed the available results and these showed that 3 ml of 0.75% solution produced very high blocks and its use was abandoned.

Duration

With both solutions, the increase in dose produced a longer duration of action (figs 3, 4). With the 0.5% solution there was no significant

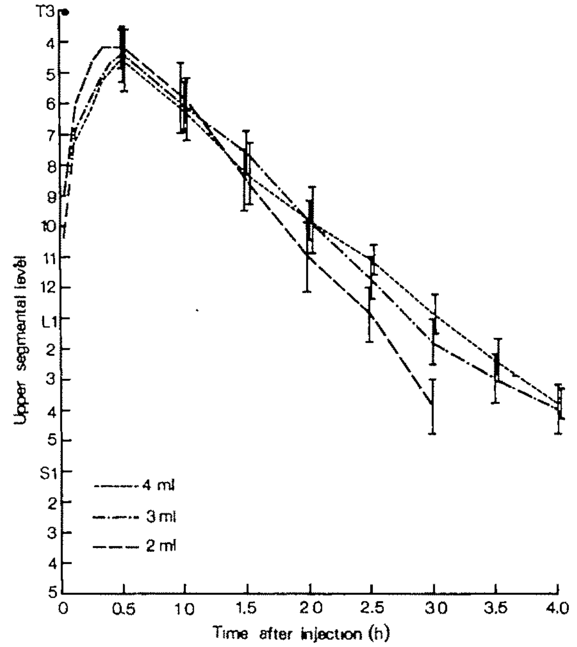

FIG. 3. Mean cephalad level of analgesia in three groups of patients who received different volumes of 0.5% bupivacaine in 8% dextrose.

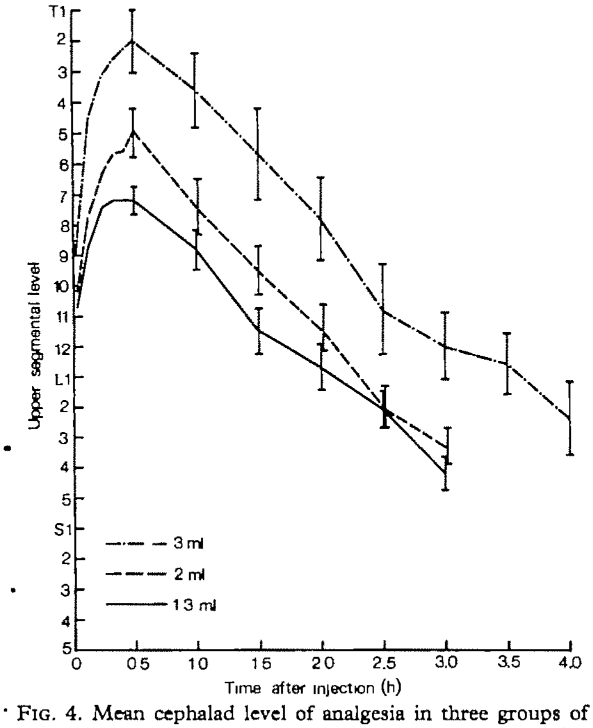

FIG. 4. Mean cephalad level of analgesia in three groups of patients who received different volumes of 0.75% bupivacaine in 8% dextrose.

difference in duration between 3 ml and 4 ml, but both these volumes produced significantly longer total durations than 2 ml. With the 0.75% solution, 3 ml produced a significantly longer duration than either 2 ml or 1.3 ml. The mean times at which analgesia was last detected in the thoracic segments, at which analgesia was no longer detectable and at which motor block had regressed to degree 0 are shown in tables IV and V. No patient was observed to have motor block after the disappearance of sensory loss.

TABLE IV. *Mean (±SEM) times (min) that sensory loss was last discernible in the thoracic segments and mean (±SEM) times (min) until no sensory loss was detected in patients who received different volumes of 0.5% bupivacaine in 8% dextrose (**P<0.001)*

Volume used	Duration of analgesia (min) In thoracic segments	Total	Motor blockade
2 ml	131±12.9	191±9.0	130±13.5
		**	
3 ml	164±11.1	225±9.2	174±14.8
4 ml	165±13.4	281±17.2	203±21.6

TABLE V. *Mean (±SEM) times (min) that sensory loss was last discernible in the thoracic segments and mean (±SEM) times (min) until no sensory loss was detected in patients who received different volumes of 0.75% bupivacaine in 8% dextrose. *P<0.05; **P<0.001)*

Volume used	Duration of analgesia (min) In thoracic segments	Total	Motor blockade
1.3 ml	108±10.7	192±13.9	118±13.4
2 ml	129±8.7	212±8.8	137±11.0
	*	**	**
3 ml	198±25.2	293±29.7	233±23.1

Side effects

One patient developed a typical post-spinal headache and responded well to an extra-dural "blood patch" on the 3rd day following operation.

Quality of surgical analgesia

One patient who underwent varicose vein surgery and who had received 4 ml of the 0.5% solution complained of pain in the region of her right knee during the operation. Although this was tolerable, she did have only patchy sensory loss in that leg. Two patients who underwent orchidectomy following transurethral resection of the prostate were given a general anaesthetic as the level of analgesia had regressed to T12 by the time that the testes were to be handled. Operating conditions were entirely satisfactory in all other patients.

DISCUSSION

Clearly, both solutions will provide satisfactory operating conditions following intrathecal administration. However, there are problems associated with the preparation of greater concentrations of bupivacaine for intrathecal use. A 1% solution will precipitate when mixed with cerebrospinal fluid and even a 0.75% solution requires careful control of the pH of the solution to avoid this. In view of this it would be justifiable to use a 0.75% solution only if it was clearly advantageous when compared with the 0.5% solution.

Comparing 1.3 ml of the 0.75% solution and 2 ml of the 0.5% solution, and 2 ml of 0.75% and 3 ml of 0.5% allows a comparison of the same dose of local anaesthetic administered in different volumes. When 15 mg was given there were no significant differences between the two solutions. When 10 mg was administered the total duration of sensory loss was similar for the two concentrations, but 1.3 ml of the 0.75% solution produced less cephalad spread than 2 ml of the 0.5% solution. However if it was considered desirable to limit the spread of sensory loss this could be produced more reliably either by using an isobaric solution or by utilizing the effects of posture on the spread of a hyperbaric solution (Wildsmith et al., 1981). An important disadvantage of the 0.75% solution was that increasing the volume administered to supine patients resulted in excessive spread. Our results failed to show any advantage in the use of 0.75% bupivacaine compared with 0.5% bupivacaine when these were administered in hyperbaric solution. The same may not apply to the use of plain solutions of bupivacaine. Wildsmith and colleagues, using amethocaine in isobaric solution, have shown that increasing the concentration and decreasing the volume administered results in the same mean level of block, but with less variation around that mean level (Wildsmith, McClure and Brown, in preparation). Increasing the volume did not result in an increase in the spread of analgesia with the 0.5% solution over the range of volumes we used and it would be interesting to find out if this held true for even larger volumes such as 4.5 ml or even 5 ml. If this was so, then the longer duration of action which these doses might be expected to produce would be useful.

In our previous study of intrathecal bupivacaine, an unusually high frequency of postoperative spinal headache was observed. We thought that this was a result of the age of the patients studied and not an effect of the drug, and this is borne out by the present study.

The mean times until the spread of sensory loss was complete was around 20 min except when only 10 mg was administered. In many studies of spinal anaesthesia assessment of the spread of sensory loss is carried out for periods of 20 min or less. If this is the case in studies of intrathecal bupivacaine, it is likely that the complete spread is not observed in all patients.

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ANESTHESIE RACHIDIENNE A L'AIDE DE BUPIVACAINE HYPERBARE: EFFETS DE LA CONCENTRATION ET VOLUME ADMINISTRE

RESUME

Lors d'une étude à double insu destinée à comparer les effets que l'on obtient en fonction des variations dans la concentration de bupivacaïne et dans le volume de la solution administrée par voie intrathécale, on a utilisé des solutions hyperbares de bupivacaïne. Cette étude a porté sur 57 patients. Dix patients ont reçu chaque volume de chaque concentration: soit 2 ml, 3 ml ou 4 ml de bupivacaïne à 0,5% dans 8% de dextrose et 1,3 ml ou 2 ml de bupivacaïne à 0,75% dans 8% dextrose. Sept autres patients ont reçu 3 ml de la solution à 0,75%. Ces deux solutions ont produit de manière suivie un bon blocage nerveux. Avec la solution à 0,5%, les

augmentations de volume administré n'ont eu aucun effet sur la dispersion de la perte sensoriell; alors qu'avec la solution à 0,75%, le fait d'augmenter le volume administré a entraîné une plus grande dispersion en direction de la tête. L'emploi de 3 ml de cette solution a été abandonné après que sept patients l'aient reçue en raison de la dispersion excessive. Avec les deux solutions, le fait d'augmenter le volume a produit une plus longue durée d'action. L'emploi d'une solution à 0,75% de bupivacaïne hyperbare pour l'anesthésie rachidienne n'a pas semblé avoir de bien grands avantages par rapport à la solution à 0,5%.

LUMBALANÄSTHESIE MIT HYPERBAREM BUPIVACAIN: AUSWIRKUNGEN DER KONZENTRATION UND DES VERABREICHTEN VOLUMENS

ZUSAMMENFASSUNG

Es wurde eine Doppelblinduntersuchung mit hyperbaren Bupivacain-Lösungen durchgeführt, um die Auswirkungen von Änderungen der Bupivacain-Konzentration und des intrathekal verabreichten Volumens zu vergleichen. Es wurden 57 Patienten studiert. Zehn Patienten bekamen jedes Volumen von jeder Konzentration: 0.5% Bupivacain in 8% Dextrose 2 ml, 3 ml oder 4 ml und 0.75% Bupivacain in 8% Dextrose 1.3 ml oder 2 ml. Weitere sieben Patienten bekamen 3 ml der 0.75%-igen Lösung. Beide Lösungen ergaben laufend gute Blockaden. Bei der 0.5%-igen Lösung hatten Steigerungen des verabreichten Volumens keinen Einfluss auf die Ausbreitung des sensoriellen Verlusts. Bei der 0.75%-igen Lösung dagegen führten Steigerungen des verabreichten Volumens zu einer bedeutend grösseren Ausbreitung in Kopfrichtung. Die Verwendung von 3 ml dieser Lösung wurde wegen der übermässigen Ausbreitungen aufgegeben, nachdem sieben Patienten sie schon bekommen hatten. Bei beiden Lösungen führten Steigerungen des Volumens zu einer länger dauernden Wirkung. Die Verwendung einer 0.75%-igen Lösung von hyperbarem Bupivacain für die Lumbalanästhesie schien keinen Vorteil gegenüber der Verwendung der 0.5%-igen Lösung zu bieten.

ANESTESIA DE LA ESPINA DORSAL CON BUPIVACAINA HIPERBARICA: EFECTOS DE LA CONCENTRACION Y DEL VOLUMEN ADMINISTRADOS

SUMARIO

Se efectuó un estudio de doble anonimato utilizando soluciones hiperbáricas de bupivacaina, para comparar los efectos de la variación de la concentración de bupivacaina y el volumen de la solución administrado intratecalmente. Se estudiaron cincuenta y siete pacientes. Diez pacientes recibieron cada uno de los volúmenes de cada concentración: al 0,5% de bupivacaina en 8% de dextrosa 2 ml, 3 ml ó 4 ml, y al 0,75% de bupivacaina en 8% de dextrosa 1,3 ml ó 2 ml. Otros siete pacientes recibieron 3 ml de la solución al 0,75%. Ambas soluciones produjeron, consistentemente, un buen bloqueo del nervio. En lo que a la solución al 0,5% respecta, el incremento del volumen administrado tuvo como consecuencia una dispersión cefálica. El uso de 3 ml de esta solución se abandonó después de que siete pacientes hubieran recibido dicha dosis, debido a la excesiva dispersión. En lo tocante a las dos soluciones, el incrementar el volumen produjo una actividad más larga. El uso de una solución de bupivacaina hiperbárica al 0,75% para la anestesia de la espina dorsal, no pareció que aportara ninguna ventaja sobre la solución al 0,5%.

Br. J. Anaesth. (1981), 54, 81

ALFENTANIL: A STUDY OF ITS ANALGESIC ACTIVITY AND INTERACTIONS WITH MORPHINE IN THE MOUSE

J. G. WILLIAMS, J. H. BROWN AND B. J. PLEUVRY

SUMMARY

Alfentanil has a short duration of action which did not markedly increase with increasing dose in mice. It is approximately one-fourth as potent as fentanyl. Repeat injections gave reproducible analgesic effects but depression of respiratory rate increased when repeat injections were given on the basis of cessation of analgesic activity. Alfentanil appeared to reduce the analgesic effect of morphine given 30–60 min after alfentanil administration. This has been demonstrated with injection of alfentanil 15 min before, simultaneously with and 30 min after morphine injection. There were no significant effects on depression of respiratory rate produced by morphine.

Alfentanil is a short-acting opioid analgesic currently undergoing pharmacological and clinical evaluation (de Castro et al., 1979; Kay and Stephenson, 1980; Niemegeers and Janssen, 1981). It has one-quarter to one-half the potency of fentanyl as an analgesic (Niemegeers and Janssen, 1981) and respiratory depressant (Brown, Pleuvry and Kay, 1980).

The present study measured the duration of analgesic action of alfentanil with increasing dose. The short duration of action makes it likely that it would be given repeatedly to the same individual and might be used to supplement the analgesic activity of another opioid such as morphine. Thus we have also examined reproducibility of repeat injections of alfentanil and interactions between alfentanil and morphine.

The laboratory mouse was used as the experimental model in these studies.

METHODS

Male Manchester strain mice, weight 25–35 g were studied. The hot-plate reaction time (Bousefield and Rees, 1969) was used to assess the antinociceptive activity of the drugs which we have equated with analgesic activity. The mouse was placed in an open-ended Perspex cylinder on a plate maintained at 55 °C. The end-point was taken as a sign of discomfort in the rear paws. Any mouse not reacting within 45 s was removed from the surface of the plate. Respiratory rate was measured using a respiratory interval timer (Crossland et al., 1977). The mouse's snout was held in the barrel of a 5-ml plastic syringe cut to a length of 2 cm. A bead thermister heated to 10 °C above ambient temperature was fitted into the luer outlet of the syringe and sensed the temperature change caused by breathing. This was displayed as respiratory interval in ms and converted to respiratory rate.

Dose-effect relationships were determined for alfentanil and fentanyl on the hot-plate reaction-time test. Analgesia was measured at 2 min intervals and, after initial studies to determine the doses, the experiments were performed blind.

From the results of this study, alfentanil 0.6 mg kg^{-1} was selected for the study of repeat doses and interaction with morphine. In the repeat dose study, alfentanil 0.6 mg kg^{-1} was administered up to a total of five times. After each dose, the hot-plate reaction-time was assessed at 2-min intervals until it had returned to saline control values. The next dose of alfentanil 0.6 mg kg^{-1} was then administered. Respiratory rate was measured just before each assessment of hot-plate reaction time. Alfentanil 0.6 mg kg^{-1} was administered either 15 min before, simultaneously with or 30 min after morphine hydrochloride. In the first two instances, the dose of morphine was 5 mg kg^{-1} and 10 mg kg^{-1} in the last so that significant analgesia was present at 90 min. Respiratory frequency was again measured just before the hot-plate reaction time.

Since there are diurnal and batch variations in the actual reaction times produced by a group of mice, all comparisons were made on concurrently

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tested mice. In experiments where only one or two mice could be handled at once, for example for comparison of the fentanyl and alfentanil dose–response curves, the order in which each dose was administered in each batch of 12 mice was randomized from batch to batch. All experiments included concurrently tested saline-treated control mice and all drugs were given i.p. in a dose volume of 0.1 ml per 10 g body weight. Results are expressed as means ± SEM in groups of 12 mice. Significance was assessed using Student's *t* test or the Mann–Whitney *U* test.

RESULTS

Alfentanil produced a dose-dependent increase in hot-plate reaction time (fig. 1) and was approximately one-quarter the potency of fentanyl. The short duration of action of alfentanil was not greatly enchanced with greater doses (fig. 2) which contrasts with the action of fentanyl in mice (fig. 3).

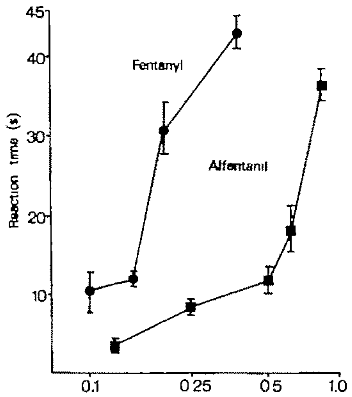

FIG. 1. Comparison of the effect of alfentanil and fentanyl on hot-plate reaction time in mice. Results are expressed as the mean ± SEM maximum reaction time ($n = 12$).

Alfentanil produced similar increases in hot-plate reaction time with each of the five repeat injections (fig. 4). The duration of analgesia was 16.8 ± 2.3 min with injection 1 and 18.3 ± 2.3 min with injection 5 indicating that there had been no prolongation of effect with repeat injections. Depression of respiratory rate was reproducible with the first three repeat doses but, subsequently, was greater than that of concurrently tested saline control mice just before injections 4 and 5 (table I).

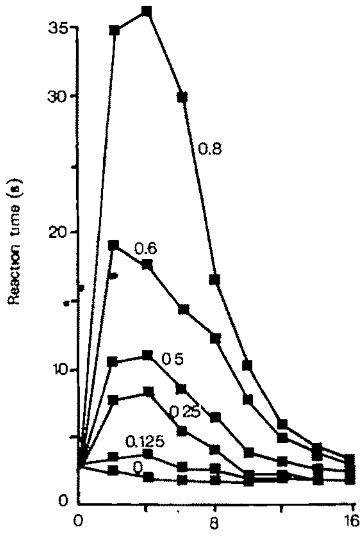

FIG. 2. Time-course of the effects of increasing doses of alfentanil on hot-plate reaction time in mice. Doses are mg kg^{-1} i.p. The points are mean responses from 12 mice.

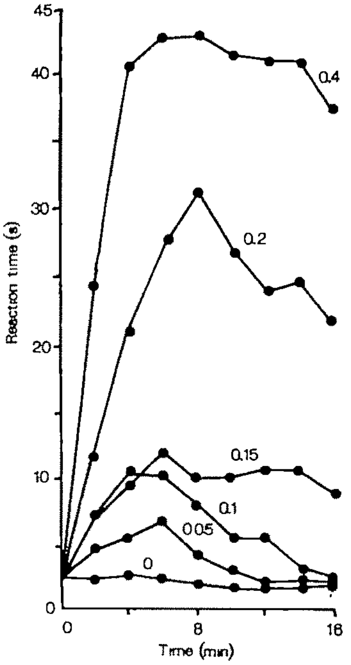

FIG. 3. Time-courses of the effects of increasing doses of fentanyl on hot-plate reaction time in mice. Doses are mg kg^{-1} i.p. The points are mean responses from 12 mice.

When alfentanil was injected simultaneously with morphine, not only was the peak analgesia less than when alfentanil was given alone, but the

TABLE I. *Effect of repeat injections of alfentanil on respiratory rate of the mouse (mean ± SEM; n = 12). *Significantly different from saline values at time 0; before next injection. The time interval between doses depended on the duration of analgesia (see text)*

Time after injection	% Change from before drug	
	Alfentanil 0.6 mg kg^{-1}	Saline 0.1 ml per 10 g
(Before drug)	250.3 ± 15.5	234.7 ± 11.4
Injection 1		
1 min	−21.5 ± 4.5	+0.1 ± 3.6
3 min	−27.2 ± 4.3	−8.0 ± 3.1
5 min	−26.4 ± 6.8	+0.3 ± 5.3
7 min	−28.6 ± 6.2	−1.9 ± 5.2
9 min	−25.0 ± 6.1	−9.6 ± 6.0
Injection 2		
0 min	−13.9 ± 5.2	−12.7 ± 4.8
1 min	−24.7 ± 6.3	−7.4 ± 4.2
3 min	−29.9 ± 7.0	−7.6 ± 4.4
5 min	−34.3 ± 5.1	−10.4 ± 3.3
7 min	−30.4 ± 6.1	−8.5 ± 5.2
9 min	−33.4 ± 3.7	−10.3 ± 6.1
Injection 3		
0 min	−16.7 ± 7.4	−9.9 ± 5.3
1 min	−36.7 ± 5.1	−6.9 ± 5.3
3 min	−39.2 ± 5.5	−10.2 ± 5.5
5 min	−39.6 ± 4.8	−9.3 ± 3.9
7 min	−41.9 ± 4.7	−11.3 ± 6.0
9 min	−37.1 ± 4.6	−4.0 ± 4.7
Injection 4		
0 min	−22.7 ± 4.8*	−6.2 ± 3.7
1 min	−33.1 ± 5.0	−11.1 ± 6.8
3 min	−37.8 ± 5.1	−3.9 ± 5.4
5 min	−38.2 ± 4.4	−5.5 ± 6.6
7 min	−34.3 ± 5.3	−10.3 ± 4.9
9 min	−37.4 ± 4.7	−1.4 ± 5.8
Injection 5		
0 min	−26.4 ± 5.3*	−2.2 ± 5.4
1 min	−37.2 ± 5.7	−5.9 ± 7.8
3 min	−38.7 ± 6.3	+3.0 ± 9.5
5 min	−40.6 ± 4.7	−11.4 ± 5.2
7 min	−40.7 ± 5.8	−2.5 ± 6.4
9 min	−34.5 ± 6.6	−0.1 ± 7.3

mice exhibited less analgesia 30–60 min after injection than those given morphine alone (fig. 5). The apparent inhibition of morphine analgesia was also seen when alfentanil was administered 30 min after the morphine or 15 min before the morphine (table II). In the latter case, the analgesic action of alfentanil had virtually ceased before the injection of morphine. In these experiments depression of respiratory rate by morphine tended to be reduced 30–60 min after alfentanil, but this was never statistically significant. To examine alfentanil-, fentanyl-, alfentanil plus fentanyl- and saline-treated mice concurrently,

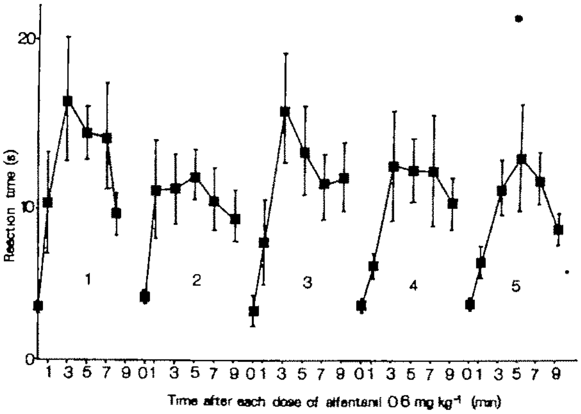

FIG. 4. Effect of repeat injections of alfentanil on hot-plate reaction time in mice. Each repeat dose was given when reaction times had returned to saline control values. Results are means ± SEM of 12 mice.

TABLE II. *Effect of alfentanil 0.6 mg kg^{-1} on the increase in hot-plate reaction time produced by morphine in the mouse. Significantly different from morphine alone: *P < 0.05; **P < 0.01 (Mann-Whitney U test). Saline and alfentanyl controls have been omitted for brevity*

Time after morphine (min)	Reaction times (mean ± SEM, n = 12)	
(A) Alfentanil after morphine		
	Morphine 10 mg kg^{-1} + saline at 30 min	Morphine 10 mg kg^{-1} + alfentanil at 30 min
0	2.27 ± 0.21	2.23 ± 0.25
15	5.42 ± 0.66	4.60 ± 0.60
35	8.33 ± 1.60	14.38 ± 2.38
40	8.29 ± 1.07	9.21 ± 1.05
45	7.08 ± 1.51	7.71 ± 1.40
60	6.98 ± 1.41	5.40 ± 1.19
75	4.85 ± 0.54	3.08 ± 0.66*
90	4.69 ± 0.81	2.15 ± 0.27**
(B) Alfentanil before morphine		
	Saline at −15 min + morphine 5 mg kg^{-1}	Alfentanil at −15 min + morphine 5 mg kg^{-1}
0	2.46 ± 0.23	2.50 ± 0.19
15	4.88 ± 0.33	3.58 ± 0.5**
30	5.04 ± 0.49	2.83 ± 0.36**
45	3.71 ± 0.36	2.33 ± 0.24**
60	3.71 ± 0.36	1.54 ± 0.10**
75	2.88 ± 0.34	1.67 ± 0.49**
90	2.42 ± 0.45	1.38 ± 0.09**

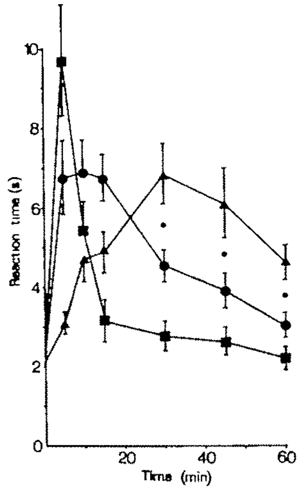

FIG. 5. Effect of simultaneous injection of alfentanil 0.6 mg kg^{-1} and morphine 5 mg kg^{-1} in mice (●). Control mice given saline and morphine 5 mg kg^{-1} (▲) and saline and alfentanil 0.6 mg kg^{-1} (■) are shown but saline controls have been omitted for clarity. Results are means ± SEM of 12 mice.

the time interval between readings in these experiments was 5 min, not 2 min as in previous experiments.

DISCUSSION

Alfentanil has been shown in the mouse to have an analgesic potency one-quarter of fentanyl. This confirms the findings of Niemegeers and Janssen (1981) in the rat. The duration of action of alfentanil was markedly less than that of fentanyl and did not increase greatly with increasing dose. Even the largest dose of alfentanil used (0.8 mg kg^{-1}) produced analgesia for only 16 min. In contrast, the largest dose of fentanyl (0.4 mg kg^{-}) has been shown to produce significant analgesia in the mouse for up to 60 min (Smith, 1976), whilst the smaller doses (0.05 mg kg^{-1}) produced a duration of analgesia comparable to that of alfentanil.

An analgesic drug of such short duration of action as alfentanil is likely to be given clinically in repeat doses. Up to five repeat doses have been shown to give reproducible analgesic effects in the mouse with no evidence of either cumulation or tolerance. However, some suggestion of cumulation was found with depression of respiratory rate which became significant after the third injection. Some cumulation with increase in arterialized venous $P\text{CO}_2$ has been reported after repeat injections of alfentanil in the rabbit (Brown, Pleuvry and Kay, 1980). In the present mouse study, as in probable clinical use, alfentanil administration was repeated after cessation of analgesic action. Thus results in mice and rabbits suggest that, if alfentanil is used repeatedly, the possibility of cumulative respiratory depression cannot be ruled out.

Alfentanil has been shown to reduce the analgesic activity of morphine in the mouse. This is unlikely to be simply a pharmacokinetic phenomenon, as similar findings were obtained when alfentanil was administerd before, simultaneously with or after morphine. It is possible that alfentanil has morphine antagonist properties or, since this action is seen long after the analgesic action of alfentanil, that a metabolite of alfentanil has antagonist properties. However, the reproducibility of repeat injections of alfentanil suggests that agonist/antagonist interaction at one receptor system does not provide a complete explanation.

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ALFENTANIL: UNE ETUDE DE SON ACTIVITE ANALGESIQUE ET DE SES INTERACTIONS AVEC LA MORPHINE CHEZ LA SOURIS

RESUME

L'action de l'alfentanil est de courte durée et celle-ci n'augmente pas de façon significative avec des doses croissantes chez la souris. Sa puissance est d'environ un quart de celle du

fentanyl. Des doses répétées eurent des effets analgésiques reproductibles mais la dépression respiratoire s'est rapidement accrue lorsque l'on administrait des injections répétées en raison de la cessation de l'activité analgésique. L'alfentanil semblait faire diminuer l'effet analgésique de la morphine administrée 30–60 min après l'administration de l'alfentanil. Ceci a été démontré lorsque l'on a administré de l'alfentanil 15 min avant, simultanément avec la morphine et 30 min après l'injection de morphine. Il n'y a pas eu d'effet marquant sur la dépression du rythme respiratoire occasionné par la morphine.

ALFENTANIL: EINE STUDIE SEINER ANALGETISCHEN WIRKUNG UND SEINER WECHSELSEITIGEN BEZIEHUNGEN ZU MORPHIUM BEI MÄUSEN

ZUSAMMENFASSUNG

Alfentanil hat eine kurze Wirkungsdauer und ist etwa nur ein Viertel so wirkungsstark wie Fentanyl. Die Wirkungsdauer steigt bei Mäusen mit erhöhten Dosen nicht erkennbar an. Wiederholte Injektionen ergaben eine reproduzierbare schmerzlindernde Wirkung, doch respiratorische Dämpfungen zeigten sich zunehmend, wenn die Injektionen nach Massgabe der nachlassenden Schmerzlinderung verabreicht wurden. Alfentanil schien die analgetische Wirkung von Morphium zu reduzieren, wenn dieses 30–60 Minuten nach Alfentanil verabreicht wurde. Dies wurde demonstriert, indem Alfentanil 15 min vor, gleichzeitig oder 30 min nach der Morphiuminjektion verabreicht wurde. Das Morphium zeigte keine erkennbaren Dämpfungen der Atmung.

ALFENTANILO: UN ESTUDIO DE SU ACTIVIDAD ANALGESICA Y SUS INTERACCIONES CON LA MORFINA EN EL RATON

SUMARIO

La acción del alfentanilo es de poca duración y ésta no aumenta marcadamente con un incremento de la dosis en el ratón. Su potencia es aproximadamente de un cuarto de la del fentanilo. Inyecciones repetidas tuvieron como consecuencia efectos analgésicos reproducibles, pero aumentó rápidamente la depresión respiratoria cuando se administraban inyecciones repetidas en base al paro de la actividad analgésica. El alfentanilo parece tener un efecto reductor sobre la analgesia causada por la morfina administrada 30–60 min después de la administración del alfentanilo. Esto se demonstró mediante inyecciones de alfentanilo 15 min antes de la inyección de morfina, simultáneamente a ella y 30 min después de la misma. No hubo efectos significantes sobre la depresión del ritmo respiratorio causada por la morfina.

Br. J. Anaesth. (1982), 54, 87

PATTERN OF REDUCTION OF VENTILATORY AND OCCLUSION PRESSURE RESPONSE TO CARBON DIOXIDE BY PENTAZOCINE IN MAN

G. B. DRUMMOND, J. FISHER, A. ZIDULKA AND J. MILIC-EMILI

SUMMARY

Mean inspiratory flow, occlusion pressure and end-tidal $P\text{CO}_2$ were measured in six healthy, sitting subjects, during breathing air and rebreathing carbon dioxide, before and after pentazocine 0.5 mg kg^{-1} i.v. and again after naloxone 20 µg kg^{-1}. Pentazocine reduced the occlusion pressure and inspiratory flow responses at a given $P\text{CO}_2$ during carbon dioxide rebreathing and these effects were antagonized by naloxone. The relationship of inspiratory flow and end-tidal carbon dioxide during rebreathing was used to measure the $P\text{CO}_2$ value at which mean inspiratory flow was 1 litre s^{-1}. Occlusion pressure at this $P\text{CO}_2$ was reduced in all the subjects by pentazocine, suggesting that the generation of inspiratory flow required less muscle activity. This effect was antagonized by naloxone.

Drugs such as sedatives, narcotics and general anaesthetics are thought to cause respiratory depression by a central action. Externally imposed loads to breathing, such as an added resistance, may also cause respiratory depression (Lourenco et al., 1966), but in these circumstances, neuromuscular activity is augmented although the resultant ventilation is diminished. By occlusion of the airway and measurement of the decrease in airway pressure during an inspiratory effort, a more direct assessment of the activity of the respiratory muscles can be made (Whitelaw, Derenne and Milic-Emili, 1975). This is because no gas flow and no lung volume changes occur during the measurement and the composite action of the inspiratory muscles is transformed into decrease of airway pressure. If the inspiratory attempt starts at the same lung volume on each occasion, then the muscles will be at the same initial length, and the pressure decrease correlates well with the neural activation of the muscles (Eldridge, 1975).

The ratio of the rate of change of pressure during an occluded breath to the rate of change of lung volume during a normal breath is an index of the "effective impedance" of the respiratory system during active inspiration.

Derenne and others (1976) measured occlusion pressure and rate of change of lung volume (as mean inspiratory flow rate, $V\text{T}/T\text{I}$) during carbon dioxide rebreathing in patients anaesthetized with methoxyflurane. The average response of occlusion pressure to carbon dioxide was reduced less than the response of mean inspiratory flow rate. This was interpreted as an increase in effective impedance and attributed to the decreased passive compliance of the respiratory system during anaesthesia. They suggested that part of the ventilatory depression observed during anaesthesia was the result of the reduced compliance of the respiratory system. In animals, however, ventilatory depression or stimulation are not associated with changes in effective impedance (Goldberg and Milic-Emili, 1977; Bopp et al., 1979).

We have studied the effects of pentazocine in conscious subjects to determine if the ventilatory depression was associated with a change in effective impedance.

METHODS

Six healthy male volunteers were studied after written consent. The study was approved by the Montreal General Hospital Ethics Committee. No subject was taking medication or had taken drinks containing caffeine for 12 h before. One subject (PB) smoked 20 cigarettes daily. Each subject was studied 2–3 h after a light non-fatty breakfast. Vital capacity and forced expiratory volume in 1 s were measured with the subject

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standing. Functional residual capacity (FRC) was measured in the sitting position in a constant volume body plethysmograph (Warren Collins). The subject then left the plethysmograph and sat comfortably with the arms supported in a carefully standardized position in an adjustable chair. He wore a noseclip, and breathed through the apparatus mouthpiece.

The apparatus consisted of two one-way valves connected to taps to allow either air breathing or rebreathing from a bag in box system (fig. 1). A pneumotachograph (Fleisch no. 2) was connected so that inspiratory flow could be measured in both circumstances using a Hewlett–Packard 270 transducer. This position allowed only room air to pass through the pneumotachograph, which was not heated. Inspired volume was derived by electrical integration of the inspiratory flow signal (Hewlett–Packard 8815A). The inspiratory and expiratory flow resistances of the apparatus were 0.14 and 0.15 kPa litre^{-1} s respectively at a flow rate of 3 litre s^{-1}. Gas was sampled at the mouthpiece with a mass spectrometer (Medspect MS8) to allow measurement of end-tidal $P\mathrm{CO_2}$ ($P\mathrm{E}'_{\mathrm{CO_2}}$) and $P\mathrm{O_2}$ to check that hyperoxia was present throughout the rebreathing manoeuvre.

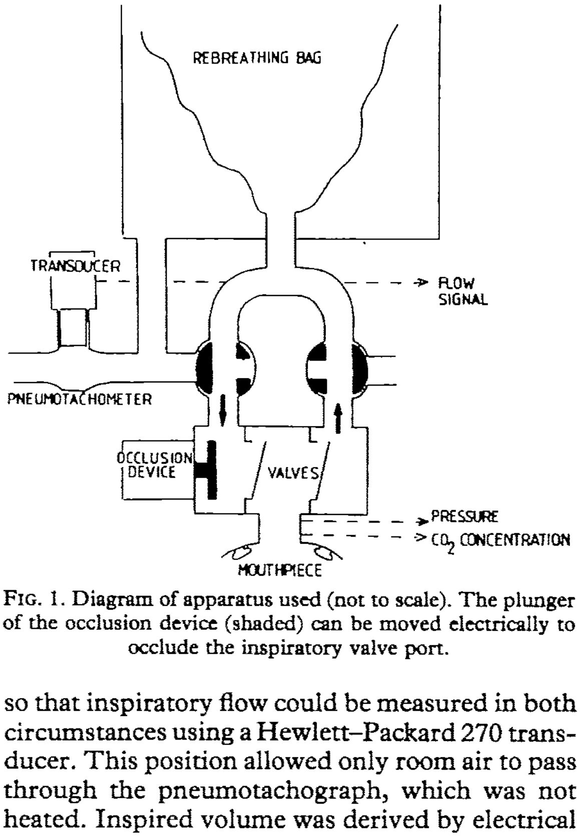

FIG. 1. Diagram of apparatus used (not to scale). The plunger of the occlusion device (shaded) can be moved electrically to occlude the inspiratory valve port.

A pneumatically-damped solenoid was used to move a piston to close the channel of the inspiratory valve. The piston movement could not be seen or heard by the subject.

The solenoid was activated during expiration without the knowledge of the subject, to prevent inspiratory flow during the early part of the next inspiratory effort. The expiratory valve was adjusted and checked to make sure that no return flow could occur during this inspiratory attempt. The resultant subatmospheric pressure was measured at the mouthpiece (Hewlett–Packard 267B transducer) and recorded on FM magnetic tape. The piston was withdrawn from the inspiratory port after about 300 ms of the effort and the delayed inspiration started, and in this way the rhythm of breathing was not greatly disturbed. The frequency response of the pressure measurement system was linear to 20 Hz.

The flow, pressure, volume and carbon dioxide concentration signals were processed and displayed on a chart recorder. An electrocardiogram taken from chest leads was displayed continuously on an oscilloscope and arterial pressure measured intermittently by sphygmomanometer.

After the subject had breathed from the mouthpiece until $P\mathrm{E}'_{\mathrm{CO_2}}$ was constant, 10 airway occlusions were performed at random intervals, each separated by at least 10 normal breaths. The taps of the apparatus were then turned to allow rebreathing, and random occlusions made at intervals of about 10 breaths during rebreathing. The bag volume was adjusted to about half the subject's vital capacity. The bag was filled with 50% oxygen, 7% carbon dioxide and nitrogen.

After a practice run, a control series of measurements were made. A slow i.v. infusion of sodium chloride 154 mmol litre^{-1} was then started and pentazocine 0.5 mg kg^{-1} given i.v. over a 5-min period, while arterial pressure was checked. Ten minutes later, the subject was moved into the body plethysmograph and FRC was measured again. He returned from the box and a further series of measurements of occlusion pressure and ventilation was made during air breathing and rebreathing. About 30 min after the pentazocine had been given, naloxone 20 µg kg^{-1} was given i.v. over a 5-min period and all measurements were repeated for a third time 10 min later.

Measurements were taken from the rebreathing records after the increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ had become linear. Measurements were made from the breath preceding the airway occlusion (fig. 2). The

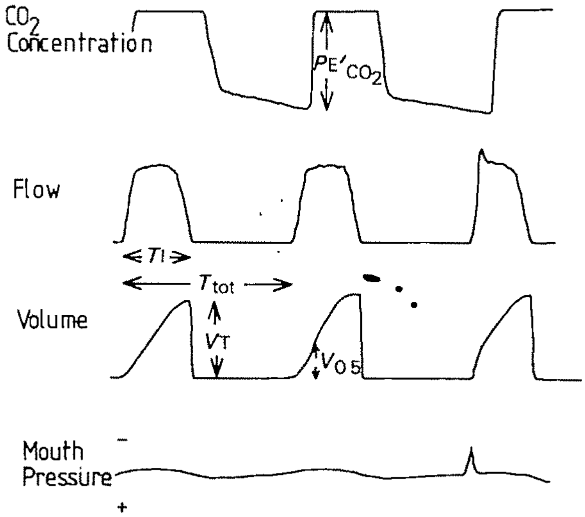

FIG. 2. A typical record showing the measurements made. T_I = inspiratory time; T_{tot} = total cycle duration; V_T = tidal volume; $V_{0.5}$ = volume inspired in 0.5 s. An occlusion has been performed at the onset of the third inspiration.

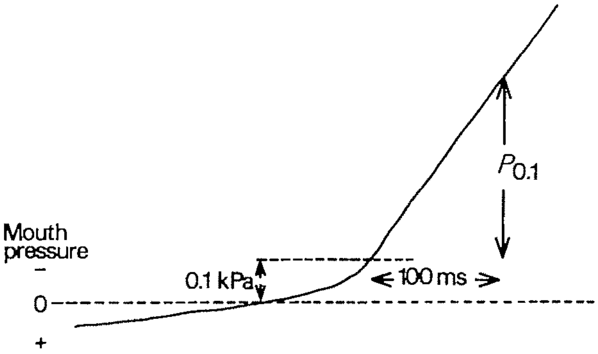

FIG. 3. A typical pressure record showing the measurements made.

duration of inspiration (T_I) was measured from the flow record. The end of the respiratory cycle was measured from the pressure trace to allow measurement of the total cycle duration (T_{tot}). The pressure trace was used to indicate the end of expiration, since inspiratory flow was occluded in the following breath. Inspired tidal volume (V_T) and the volume inspired in the first 0.5 s of inspiration ($V_{0.5}$) were measured from the volume trace. Inspiratory minute volume ($\dot{V}_I$) was calculated as $V_T \times 60 \times 1/T_{tot}$ and was not corrected to BTPS. Mean inspiratory flow was calculated as V_T/T_I.

The pressure signal was replayed from the tape recording to the chart recorder at the end of the experiment to allow part of the chart record to be made at a suitable speed for measurement of occlusion pressure (50 mm s^{-1}). This avoided making changes in recorder speed during the experiment which could have warned the subject that an airway occlusion was imminent.

Occlusion pressure was measured 100 ms after the airway pressure had become less than -0.1 kPa ($P_{0.1}$) rather than after the pressure became less than atmospheric (fig. 3). This method is similar to that advocated by Kryger, McCullough and Weil (1976) who measured the pressure change from 50 to 100 ms after the pressure became less than atmospheric. Occlusion pressure was also measured by the original method of Whitelaw, Derenne and Milic-Emili (1975).

The mean values of the measured and derived variables during air breathing were compared using Student's *t* test for paired values. Linear regression relationships for the values obtained during rebreathing were calculated by the least squares technique. Occlusion pressure values at an inspiratory flow rate of 1 litre s^{-1} were estimated from the linear regression relationship of mean inspiratory flow $P_{E'CO_2}$, and the logarithm of occlusion pressure with $P_{E'CO_2}$. These values were compared using the Wilcoxon signed rank test.

RESULTS

Details of subjects are given in table I. Subject JF had a moderately reduced FRC and RV.

No significant changes in breathing pattern were found after pentazocine or naloxone when the subjects breathed air. Mean $P_{E'CO_2}$ in the control state was 5.95 kPa ± 0.62, and this

TABLE I. *Details of subjects studied. $FEV_{1.0}$ = forced expiratory volume in 1 s; VC = vital capacity; RV = residual volume; FRC = functional residual capacity; FVC = forced vital capacity*

Subject	Age (yr)	Height (m)	Weight (kg)	$FEV_{1.0}$/FVC (%)	VC (% predicted)	RV (% predicted)	FRC (% predicted)
AZ	36	1.78	79	71	119	100	96
RR	27	1.79	85	80	115	97	96
JF	25	1.85	90	74	95	65	76
PB	30	1.75	63	77	99	93	99
BH	28	1.72	74	78	110	88	89
RD	22	1.80	68	93	99	83	94

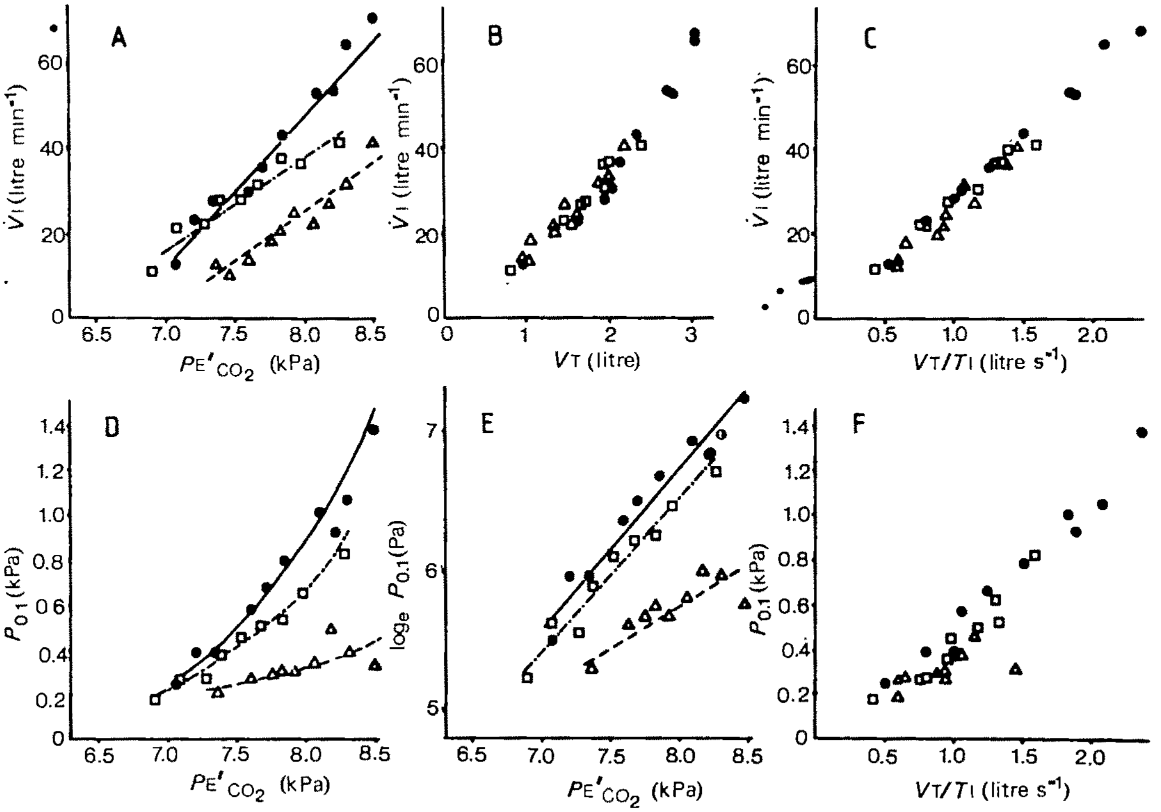

FIG. 4. Results of rebreathing procedure in a representative subject. Each point represents a single measurement. ● = control measurements; △ = after pentazocine; □ = after naloxone.

increased by 0.59 kPa ($P<0.001$) after pentazocine and decreased by 0.64 kPa ($P<0.001$) after naloxone. The values after naloxone were not significantly different from control. No significant change in FRC was detected after pentazocine administration.

The results obtained from rebreathing experiments in an individual subject (AZ) are shown in figure 4. Pentazocine reduced the ventilatory response to $P\text{E}'_{\text{CO}_2}$ and displaced the relationship towards greater $P\text{E}'_{\text{CO}_2}$ values (panel A). Naloxone returned the relationship towards control values. Panel B shows the relationship of $\dot{V}$I to VT. There is no apparent difference between the three sets of measurements. In panel C, the relationship between $\dot{V}$I and VT/TI is linear for the control state and after drug administration. However, the values of $\dot{V}$I for a given VT/TI value are less after pentazocine administration ($P<0.05$). This change in relationship was accompanied by a reciprocal change in the duration of inspiration (TI) relative to the

TABLE II. *Mean values and standard deviation for relative duration of inspiration ($T\text{I}/T_{\text{tot}}$) during carbon dioxide rebreathing*

Subject	Control	After pentazocine	After naloxone
AZ	0.48±0.03	0.41±0.06	0.47±0.02
RR	0.49±0.04	0.53±0.09	0.50±0.02
JF	0.44±0.03	0.42±0.07	0.44±0.03
PB	0.47±0.02	0.42±0.02	0.44±0.03
BH	0.44±0.03	0.45±0.03	0.45±0.04
RD	0.48±0.03	0.49±0.04	0.48±0.02

TABLE III. *Ratio of volume inspired in 0.5 s ($V_{0.5}$) to mean inspiratory flow ($V\text{T}/T\text{I}$) during rebreathing (mean ± SD)*

Subject	Control	Pentazocine	Naloxone
AZ	0.52±0.04	0.60±0.05	0.62±0.05
RR	0.53±0.04	0.47±0.05	0.53±0.05
JF	0.52±0.06	0.56±0.05	0.49±0.06
PB	0.58±0.05	0.51±0.09	0.51±0.03
BH	0.51±0.06	0.50±0.05	0.47±0.07
RD	0.59±0.04	0.60±0.05	0.62±0.05

TABLE IV. *Regression relationships of mean inspiratory flow rate ($V\text{T}/T\text{I}$) with $P\text{E}'_{CO_2}$ and $l_n P_{0.1}$ with $P\text{E}'_{CO_2}$. C = control; P = after pentazocine; N = after naloxone. *Predicted value is based upon extrapolation of the relationship to 7 kPa*

		$V\text{T}/T\text{I}$ v. $P\text{E}'_{CO_2}$			$\log P_{0.1}$ v. $P\text{E}'_{CO_2}$		
Subject	State	Slope (litre s^{-1} kPa^{-1})	Predicted value when $P\text{E}'_{CO_2} = 7$ kPa (litre s^{-1})	r	Slope (ln Pa kPa^{-1})	Predicted value when $P\text{E}'_{CO_2} = 7$ kPa (ln Pa)	r
AZ	C	1.32	0.98	0.98	1.47	5.80	0.96
	P	0.79	0.52	0.96	0.85	4.92	0.76
	N	0.82	0.92	0.97	1.56	5.48	0.97
RR	C	1.22	1.49	0.98	1.80	6.04	0.90
	P	0.51	0.63	0.95	1.01	4.43	0.67
	N	1.07	1.78	0.98	1.53	6.50	0.97
JF	C	0.97	0.80	0.97	0.66	6.33	0.95
	P	1.01	0.21	0.99	0.27	5.80	0.41
	N	1.21	0.95	0.99	1.03	6.30	0.86
PB	C	0.60	0.60	0.98	1.18	5.27	0.42
	P	0.65	0.19*	0.99	1.28	4.21	0.96
	N	0.63	0.52	0.98	0.72	5.15	0.96
BH	C	0.84	2.09*	0.99	1.00	7.18	0.94
	P	0.43	1.42*	0.84	0.37	5.92	0.63
	N	0.65	1.86*	0.98	0.72	6.82	0.92
RD	C	0.78	0.52*	0.98	0.91	5.42	0.99
	P	0.57	0.37*	0.94	0.77	4.98	0.87
	N	0.76	0.74*	0.95	0.97	5.66	0.90

duration of the total respiratory cycle (T_{tot}). The ratio $T\text{I}/T_{tot}$ decreased from a mean of 0.48 to 0.41 after pentazocine and increased to 0.47 after naloxone in this subject. (Ventilation is proportional to the product of $V\text{T}/T\text{I}$ and $T\text{I}/T_{tot}$.) The changes in $T\text{I}/T_{tot}$ in the six subjects were not consistent (table II) and a statistically significant change was only found in one subject (PB).

The relationship of $V_{0.5}$ and $V\text{T}/T\text{I}$ did not change significantly in any of the subjects with drug administration. The ratio of these values remained close to 0.5, indicating that the inspiratory waveform remained linear (table III).

The relationship between $P_{0.1}$ and $P\text{E}'_{CO_2}$ was not linear (panel D), whereas that between log $P_{0.1}$ and $P\text{E}'_{CO_2}$ appeared to be so (panel E). In five of the six subjects, the correlation of log $P_{0.1}$ with $P\text{E}'_{CO_2}$ was greater than that of $P_{0.1}$ with $P\text{E}'_{CO_2}$. The relationship of $P_{0.1}$ with $V\text{T}/T\text{I}$ (panel F) shows that, for a given value of $V\text{T}/T\text{I}$, $P_{0.1}$ values after pentazocine were less than the $P_{0.1}$ values in the control state.

Table IV gives the details of the linear regression relationships of both $V\text{T}/T\text{I}$ and log $P_{0.1}$ with $P\text{E}'_{CO_2}$ for each subject in each state, and these relationships are shown in figures 5 and 6. The relationship between $V\text{T}/T\text{I}$ and $P\text{E}'_{CO_2}$ was displaced towards greater values of $P\text{E}'_{CO_2}$ in all subjects after pentazocine and in four (RR, AZ, BH and RD), the slope was less than in the control state. (In three of these subjects, the mean value for $T\text{I}/T_{tot}$ was increased after pentazocine, whereas in the other subjects it decreased.) The pattern of change in the relationship of log $P_{0.1}$ with $P\text{E}'_{CO_2}$ caused by pentazocine and naloxone (fig. 6) resembled the changes found in the relationship of $V\text{T}/T\text{I}$ with $P\text{E}'_{CO_2}$ except in subject PB.

The $P_{0.1}$ values associated with a mean inspiratory flow of 1 litre s^{-1} were less after pentazocine than in the control state ($P<0.05$) whereas those

TABLE V. *Values of $P_{0.1}$ (kPa) predicted from linear regression relationship of ln $P_{0.1}$ with $P\text{E}'_{CO_2}$, using $P\text{E}'_{CO_2}$ values that would give a mean inspiratory flow rate of 1 litre s^{-1}*

Subject	Control	After pentazocine	After naloxone
AZ	0.61	0.42	0.51
RR	0.37	0.31	0.40
JF	1.16	0.74	1.03
PB	0.77	0.60	0.54
BH	0.66	0.47	0.64
RD	0.72	0.63	0.73

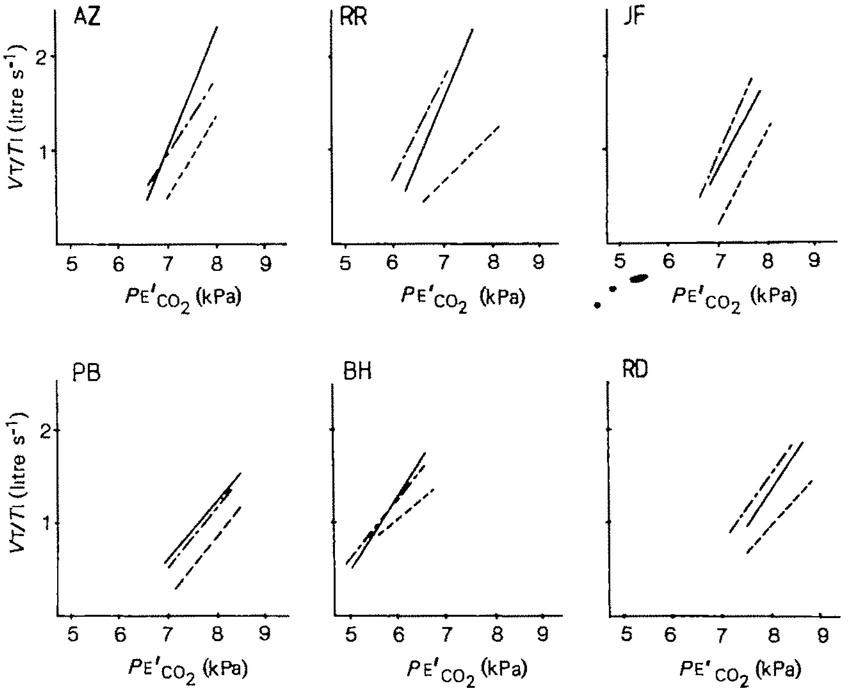

FIG. 5. Individual linear regression relationships of mean inspiratory flow (V_T/T_I) with $P_{E'CO_2}$. —— = control measurements; - - - = after pentazocine; — - — - = after naloxone.

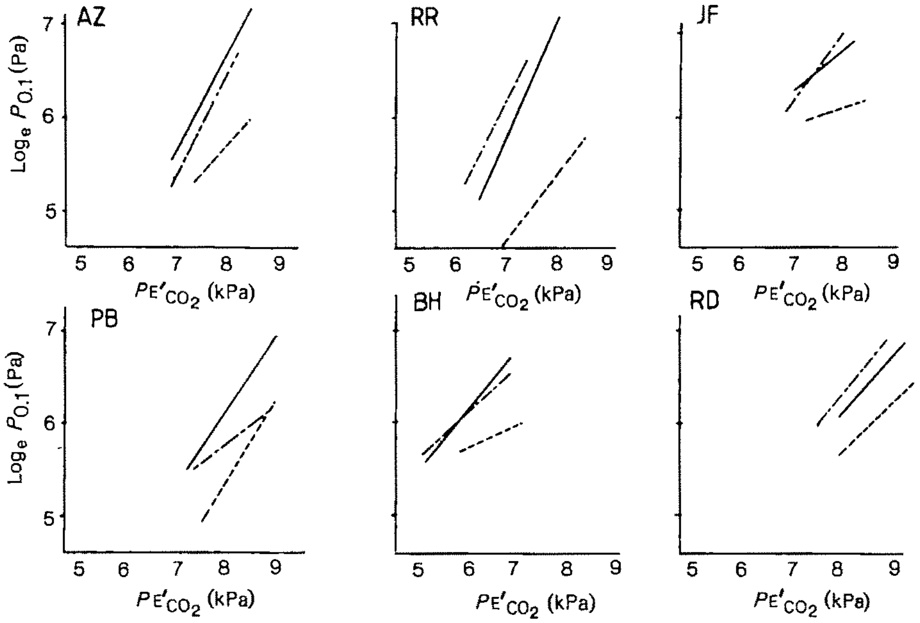

FIG. 6. Individual linear regression relationships of log $P_{0.1}$, with $P_{E'CO_2}$ (same symbols as in figure 4).

after naloxone were not significantly different from control (table V).

DISCUSSION

Methods

This study was undertaken to determine if the relationship of occlusion pressure and mean inspiratory flow was altered after ventilatory depression. A dose of pentazocine was selected that caused significant depression (Belville and Green, 1965) and a dose of naloxone that would antagonize this (Kallos and Smith, 1968). All the subjects were able to detect when pentazocine had been given. We did not believe that a blind study would have shown different effects since we studied breathing during stimulation by rebreathing carbon dioxide. Naloxone was used to show that the changes caused by pentazocine could be reversed and that the changes were not a result of the sequence of the study. Naloxone does not influence respiration in normal subjects when given alone (Evans et al., 1974; Fleetham et al., 1980).

Inspection of the recording of the pressure signal showed that the occlusion pressure wave had a variably gradual onset. The exact time at which airway pressure became less than atmospheric was difficult to define because the rate of change of pressure was small. However, the time at which the pressure became less than 0.1 kPa below atmospheric was easy to define and in this study, $P_{0.1}$ was measured as the pressure change in the subsequent 100 ms. The time taken for the airway pressure to decrease from atmospheric to -0.1 kPa varied from subject to subject. It decreased as $P_{0.1}$ increased in each subject. Measurements of occlusion pressure by our method were less variable and had a better correlation with $P\text{E}'_{CO_2}$ than measurements made by the original method of Whitelaw, Derenne and Milic-Emili (1975), so we used these values for analysis. In other rebreathing experiments in man (Drummond and Danylewick, unpublished data) measurements made from -0.1 kPa correlated more closely with the pressure decrease from 50 to 100 ms used by Kryger, McCullough and Weil (1976). Drummond and Scott (1980) suggested that the gradual decrease in pressure at the onset of the occlusion pressure wave in man was caused by the compliance of the upper airway.

Results

Neural activation of the inspiratory muscles increases progressively during inspiration. If the airway is occluded, the contraction of the muscles is isometric and the pressure generated indicates the magnitude of the neural activation, as long as the initial muscle length is the same on each occasion. The pressure produced is greater than the pleural pressure change that occurs when the muscles are allowed to shorten in a normal breath, because of the length–tension characteristics of active muscle (Mognoni et al., 1968).

If the volume inspired at the end of a normal inspiration is compared with the pressure produced after the same duration of an occluded effort, the "effective elastance" of the respiratory system can be calculated. This value is measured at zero flow and represents the sum of the passive elastic properties of the respiratory system, the intrinsic length–tension characteristics of the muscles, and possibly neural reflex components (Eldridge and Vaughn, 1977). This "effective elastance" allows prediction of the response of the respiratory system to external loads, whereas the passive elastance does not (Lynne-Davies et al., 1971).

In conscious subjects, occlusion pressure cannot be reliably measured for more than about 150 ms since the effort becomes altered by conscious influences (Whitelaw, Derenne and Milic-Emili, 1975). Consequently, occlusion pressure cannot be measured at a time equivalent to the end of a normal inspiration, and effective elastance cannot be measured. Measurement of $P_{0.1}$ is made when the inspiratory muscles would normally be generating inspiratory flow as well as volume change. Consequently the relationship of $P_{0.1}$ with mean inspiratory flow rate ($V\text{T}/T\text{I}$) is an index of "effective impedance" which is a value that contains both elastic and resistive components.

The relationship of $P_{0.1}$ with $V\text{T}/T\text{I}$ is not constant as ventilation is increased. We found that $V\text{T}/T\text{I}$ increased linearly with increasing $P\text{E}'_{CO_2}$, as shown by Barcroft and Margaria (1931). However we found that $P_{0.1}$ increased exponentially with increasing $P\text{E}'_{CO_2}$ as found by others (Whitelaw, Derenne and Milic-Emili, 1975; Zackon, Despas and Anthonisen, 1976). This exponential relationship is probably because airway resistance increases exponentially as inspiratory flow increases (Cotes, 1975). Because $V\text{T}/T\text{I}$ and $P_{0.1}$

are not related to $P\text{E}'_{CO_2}$ in the same way, they will not bear a constant relationship to each other and the "effective impedance" of the respiratory system will increase with increasing inspiratory flow (as does airway resistance). Consequently, we chose to compare $P_{0.1}$ values that were associated with identical mean inspiratory flow rates before and after drug administration, so that the pressure component related to flow would be similar. This pressure component could change if airway resistance were to change, but pentazocine does not influence bronchomotor tone (Aviado, 1975) and we found no change in FRC that could have altered airway resistance.

Occlusion pressure is measured early in inspiration and mean inspiratory flow is calculated from values measured at the end of inspiration. Their relationship could be changed by change in the pattern of the increasing activation of the respiratory muscles leading to a change in the pressure and volume wave forms. However, the ratio of the volume inspired in the first 0.5 s of inspiration with the rate of volume inspired over the whole of inspiration ($V\text{T}/T\text{I}$) was similar in all the subjects and did not change after pentazocine, showing that the pattern of increase in muscle activation did not alter.

In animals, a change in FRC has been shown to alter the occlusion pressure produced by the same amount of neural activation because the initial length and shape of the muscles has been changed (Eldridge and Vaughn, 1977). However, Burki (1977) found that the relationship of $P_{0.1}$ to $P\text{E}'_{CO_2}$ in man was not influenced by moving subjects from the seated to the supine position despite a mean decrease in FRC of 0.8 litre. The method of FRC measurement used in the present study could detect an FRC change of 0.4 litre. Even if the relationship of $P_{0.1}$ to neural drive were altered by changes in this range, this would only preclude estimation of neural drive from $P_{0.1}$ values. The relationship of $P_{0.1}$ with inspiratory flow would still indicate the effective mechanics of the respiratory system.

We found that a smaller $P_{0.1}$ was associated with the same inspiratory flow rate after pentazocine, suggesting that the effective elastance of the respiratory system had decreased. The passive elastic properties were unlikely to have changed since pentazocine does not influence the elastance of the respiratory system even in larger doses (Hanato et al., 1975) and FRC is unlikely to have changed enough to alter elastance significantly.

Other workers have reported relative changes in occlusion pressure and ventilatory responses after narcotics. Kryger and others (1976) studied five normal subjects before and after a small, variable oral dose of pethidine. $P_{0.1}$ appeared to be less reduced than ventilation after pethidine during steady state hyperoxic hypercapnia and progessive isocapnic hypoxia. Kryger and others did not, however, report either the relative duration of inspiration (which would have influenced the relationship between $P_{0.1}$ and $\dot{V}\text{E}$) or the posture of the subjects. Knill and others (1976) studied supine adolescent patients after i.m. morphine or pethidine. At the same values of occlusion pressure, $V\text{T}/T\text{I}$ was less after drug administration. They suggested that this probably indicated an increase in effective respiratory impedance because of increased tonic activity of chest wall and abdominal muscles. This pattern of activity has been described during morphine and nitrous oxide anaesthesia (Sokoll, Hoyt and Gergis, 1972; Freund et al., 1973) but has not been seen after large doses of pentazocine (Hanato et al., 1975). The present study shows that pentazocine reduces the effective impedance of the respiratory system, contrary to the findings of Kryger and others (1976) and Knill and others (1976). In our subjects, the decrease in ventilation that occured was less than it would have been if the effective elastance had not changed.

The most likely explanation for these findings is that, in adult upright subjects, the sedative effect of pentazocine reduces the tonic activity of chest wall muscles and hence the muscular contribution to the stiffness of the chest wall, allowing the diaphragm to drive the ribcage more easily (Goldman, 1974; Sharp et al., 1975). However, such a decrease in effective elastance means that the respiratory system is less able to compensate if loads to breathing are imposed (Margaria et al., 1973).

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TYPE DE REDUCTION DE LA REPONSE DE LA PRESSION DE VENTILATION ET D'OCCLUSION A L'ANHYDRIDE CARBONIQUE DUE A LA PENTAZOCINE CHEZ L'HOMME

RESUME

On a mesuré chez six sujets sains en position assise le flux inspiratoire moyen, la pression d'occlusion et le $P\mathrm{CO}_2$ respiratoire terminal, au cours de la respiration d'air et d'une nouvelle respiration d'anhydride carbonique, avant et après avoir administré 0,5 mg kg^{-1} de pentazocine i.v. et de nouveau après 20 µg kg^{-1} de naxolone. La pentazocine a fait diminuer la résponse de pression d'occlusion et du flux inspiratoire à un $P\mathrm{CO}_2$ donné au cours d'une nouvelle respiration d'anhydride carbonique et ces effets ont èté antagonisès par la naxolone. Le rapport entre le flux inspiratoire et l'anhydride carbonique respiratoire terminal au cours de la nouvelle respiration a été utilisé pour mesurer la valeur du $P\mathrm{CO}_2$ à laquelle le flux inspiratoire moyen était de 1 litre s^{-1}. La pression d'occlusion à ce $P\mathrm{CO}_2$ a baissé chez tous les sujets sous l'effet de la pentazocine, ce qui suggère que la génération du flux inspiratoire exige moins d'activité musculaire. Cet effet fut antagonisé par la naxolone.

REDUKTIONSBILD DER ATMUNGSDRUCK- UND ABSCHLIESSUNGSDRUCK-REAKTION AUF KOHLENDIOXYD DURCH PENTAZOCIN BEIM MENSCHEN

ZUSAMMENFASSUNG

Mittlerer inspiratorischer Druck, Abschliessungsdruck und Endatmungs-$P\mathrm{CO}_2$ wurden bei sechs gesunden sitzenden Menschen während der Atmung von Luft und der Wiedereinatmung von Kohlendioxyd vor und nach der Verabreichung intravenösen von 0,5 mg kg^{-1} und auch nach Naloxon 20 µg kg^{-1} gemessen. Pentazocin reduzierte die

Abschliessungsdruck- und Einatmungsfluss-Reaktionen bei einem vorgegebenen $P\mathrm{CO}_2$ Wert während der Wiedereinatmung von Kohlendioxyd, und die Auswirkungen wurden durch Naloxon bekämpft. Die Verbindung zwischen inspiratorischem Fluss und Endatmungs-$P\mathrm{CO}_2$ während der Wiedereinatmung wurde verwendet, um den $P\mathrm{CO}_2$-Wert zu messen, bei dem der mittlere inspiratorische Fluss 1 litre s^{-1} entsprach. Der Abschliessungsdruck bei diesem $P\mathrm{CO}_2$-Wert wurde bei allen Versuchspersonen mittels Pentazocin reduziert, was vermuten lässt, dass die Erzeugung des inspiratorischen Flusses weniger Muskelaktivität braucht. Diese Auswirkung wurde durch Naloxon bekämpft.

CONFIGURACION DE LA REDUCCION DE LA RESPUESTA DE LA PRESION VENTILATORIA Y DE OCLUSION AL ANHIDRIDO CARBONICO POR LA PENTAZOCINA EN EL HOMBRE

SUMARIO

Se midieron el flujo inspiratorio medio, la presión de oclusión y el $P\mathrm{CO}_2$ respiratorio terminal en seis personas sentadas en el curso de la respiración de aire y de la nueva respiración de anhídrido carbónico, antes y después de administrarles 0,5 mg kg^{-1} de pentazocina i.v. y, de nuevo, después de una de 20 µg kg^{-1} de naxolona. La pentazocina redujo las respuestas de la presión de oclusión y del flujo inspiratorio en un $P\mathrm{CO}_2$ dado en el curso de una nueva respiración de anhídrido carbónico y dichos efectos se hallaron antagonizados por la naxolona. La relación entre el flujo inspiratorio y el anhídrido carbónico respiratorio terminal en el curso de la nueva respiración se usó para medir el valor del $P\mathrm{CO}_2$ en que el flujo inspiratorio medio era de 1 litro s^{-1}. La presión de oclusión en este $P\mathrm{CO}_2$ se reducía por acción de la pentazocina en todas las personas, lo que hace pensar que la generación del flujo inspiratorio necesitaba una actividad muscular menor. La naxolona antagonizó dicho efecto.

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EFFECTS OF THE INHALATION OF ENFLURANE ON HEPATIC MICROSOMAL ENZYMATIC ACTIVITIES IN THE RAT

M. G. F. DA ROCHA-REIS AND C. HIPÓLITO-REIS

SUMMARY

We have investigated the possible hepatic microsomal enzyme induction effect of enflurane, administered by inhalation in anaesthetic doses for periods of 1 h a day. In 15 experimental groups, differing from one another in anaesthetic concentration (1, 2 and 3% enflurane) and in the number of days of treatment (3, 7, 10, 14, 21 and 24) we found (1) no alteration either in the ratio of liver to body weight or in the microsomal protein content; (2) no modifications in aniline hydroxylase activity; (3) a decrease in the aminopyrine demethylase activity after a number of exposures, varying with the dose.

Inhalation anaesthetics are metabolized by microsomal enzymes, located mainly in the liver, which are also responsible for the transformation of other xenobiotics and of some endogenous products (Van Dyke, 1973; Brown, 1976; Hipólito-Reis and Rocha-Reis, 1977; Cohen, 1978). The synthesis of these enzymes can be induced by certain substances in an apparently non-specific way (Brown, 1973; Gillette, 1971). The increase in the enzyme quantity may affect the biotransformation both of the inducer itself (autoinduction) and of other substances (cross-induction). Among the enzymatic inducers we have the inhalation anaesthetics, such as diethyl ether, fluroxene, halothane, methoxyflurane and isoflurane (Berman and Bochantin, 1970; Linde and Berman, 1971; Brown and Sagalyn, 1974).

In this work, we have tried to determine the possible cross-induction capacity of enflurane, which itself is thought to be relatively resistant to biotransformation (Halsey et al., 1971; Cousins et al., 1976; Dooley et al., 1979). Previous reports on this subject are limited (Linde and Berman, 1971; Berman et al., 1976).

The results we obtained proved that, under the conditions we used, enflurane is not an enzyme inducer and they refute both the impression given by the literature that inhalation anaesthetics are generically inducers and the nowadays less plausible impression that their action on microsomal enzymic activities is a non-specific effect.

MATERIALS AND METHODS

Reagents and enzymes

All the reagents used were analar quality or the chemically purest ones available. The isocitric dehydrogenase, the isocitrate and the NADPH were supplied by Sigma (U.S.A.).

Laboratory animals

We used adult male, white Wistar rats, weights 225–300 g. These animals are supplied by the Biology Center of Fundação Calouste Gulbenkian (Oeiras), weighing approximately 100 g, and they are kept in our Laboratory under conditions of continuous renewal of atmospheric air, constant temperature and humidity, with alternate 12-h periods of light (8–20 h) and of dark. The animals were given a suitable commercial diet, which has proved to be totally satisfactory, and water *ad libitum*. No insecticides were used.

The administration of the anaesthetic took place during 1 h a day, for periods varying from 3 to 24 days. The animals were placed inside a glass container of 10-litre capacity containing soda-lime in a compartment made at the bottom with a drilled platform. There was a continuous renewal of gas atmosphere. Enflurane (Ethrane, Abbott Laboratories) was vaporized in air by an Enfluratec vaporizer (Cyprane, Ltd) and the concentration used were 1, 2 or 3%.

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After the period of anaesthesia, the rats were placed again in their usual environment and were fed *ad libitum*.

To avoid the possibility of normal variations in enzymatic activities interfering with any treatment-related effects, all observations were compared with those of control animals which were treated identically except that they did not receive enflurane.

The experiments with administration of the anaesthetic for 3 days were carried out within a short period of time, while the other took place during a longer period. The control groups are, however, contemporaneous with the experiment groups.

The rats were killed with a guillotine 24 h after the last administration of anaesthetic. The liver was removed, its weight was registered and after cooling in micronized ice, the microsomes were prepared (Schenkman, Remmer and Estabrook, 1967).

Analytical procedures

The incubation medium had the following final concentrations for both enzyme activity tests: Tris-HCl buffer 50 mmol litre^{-1}, pH 7.5; magnesium chloride 5 mmol litre^{-1}; NADPH 1 mmol litre^{-1}; isocitrate 5 mmol litre^{-1}; isocitric dehydrogenase 0.4 u. ml^{-1}; in a final volume of 5 ml. The final protein concentration was 1.5 mg ml^{-1} for the aniline hydroxylase test and 1 mg ml^{-1} for the aminopyrine demethylase test. The mixture containing the microsomal suspension and the NADPH generating preparation was thermally equilibrated for 5 min and the enzyme reaction started with the addition of substrate: 8 mmol litre^{-1} (final concentration) for aminopyrine and for aniline.

The incubations were carried out in an open atmosphere at 37 °C, in a shaking Dubnoff incubator. Specimens were removed after 0, 5, 10, 15 and 20 min. The reaction was stopped with the addition of trichloroacetic acid, 7.5% for aminopyrine and 15% for aniline, followed by the determination of formaldehyde (Nash, 1953) and of p-aminophenol (Kato and Gillette, 1965) respectively.

We had verified previously that, under the conditions used, the enzymic activity is proportional to the time of incubation, but in order that the tests could be compared it was necessary to use the same protein concentration.

The results were expressed in μmole of the product formed, per min and per mg of microsomal protein.

Protein assays

Protein contents were determined by the method of Lowry and others (1951), Lab-Trol (Dade Diagnostic, Inc., U.S.A.) being used as standard.

Statistical analysis

Significance of difference between means was assessed by Student's t test.

RESULTS

Enflurane, in different concentration in the anaesthetic mixture, inhaled for 1 h a day for a variable number of days, did not show any hepatic microsomal enzymatic induction effect of the hydroxylase activity of aniline and of the demethylase activity of aminopyrine under the experimental conditions we used (table I); on the contrary, we

TABLE I. *Effect of exposure to different concentrations of enflurane for different times, on hydroxylase activity of aniline (formaldehyde released—μmol min^{-1} per mg microsomal protein) and demethylase activity of aminopyrine (p-aminophenol—μmol min^{-1} per mg microsomal protein). * Significantly different from respective control (P < 0.05)*

Duration of exposure (days)	Demethylase activity	Hydroxylase activity
Enflurane 1%		
Control	5.271±0.749 ($n = 3$)	0.449±0.103 ($n = 7$)
3	4.859±0.752 ($n = 4$)	0.240±0.028 ($n = 4$)
Control	7.298±1.605 ($n = 6$)	0.404±0.165 ($n = 6$)
7	5.780±0.734* ($n = 4$)	0.387±0.086 ($n = 4$)
10	3.997±0.406* ($n = 4$)	0.206±0.047 ($n = 4$)
14	5.658±0.994* ($n = 4$)	0.358±0.155 ($n = 4$)
17	5.129±1.580* ($n = 4$)	0.293±0.162 ($n = 4$)
21	4.657±1.406* ($n = 4$)	0.277±0.071 ($n = 4$)
24	5.350±2.337* ($n = 4$)	0.494±0.040 ($n = 4$)
Enflurane 2%		
Control	5.271±0.749 ($n = 7$)	0.449±0.103 ($n = 7$)
3	5.197±0.968 ($n = 4$)	0.305±0.019 ($n = 4$)
Control	6.895±0.436 ($n = 7$)	0.404±0.165 ($n = 6$)
7	5.642±1.779* ($n = 4$)	0.387±0.086 ($n = 4$)
10	4.797±1.125* ($n = 4$)	0.206±0.047 ($n = 4$)
14	4.428±0.822* ($n = 4$)	0.385±0.155 ($n = 4$)
17	5.325±0.944* ($n = 4$)	0.293±0.162 ($n = 4$)
21	3.751±0.824* ($n = 4$)	0.277±0.071 ($n = 4$)
24	5.670±0.930* ($n = 4$)	0.494±0.040 ($n = 4$)
Enflurane 3%		
Control	5.271±0.749 ($n = 7$)	0.449±0.103 ($n = 7$)
3	2.706±0.100* ($n = 4$)	0.447±0.030 ($n = 4$)

found that, with inhalation for 1 h a day, there was a decrease in the demethylase activity of aminopyrine in the animals which inhaled 1 or 2% enflurane over 7 or more days or 3% enflurane over 3 days ($P < 0.05$ in all cases). However, no significant differences were observed between these experimental groups of longer duration.

The hydroxylase activity of aniline was not changed in any of the experimental groups.

We further verified that there was not any statistically significant variation in any group, either in the ratio of liver to body weight or in the hepatic microsomal protein content relative to either liver or body weight of the animal (table II).

DISCUSSION

It is well known that enzyme inducers interfere in the metabolism and in the toxicity of certain general anaesthetics. The problem has been studied particularly in relation to the renal and hepatic toxicity of halothane, fluroxene, chloroform and methoxyflurane (Shoeller, 1970; Brown, 1972; Cascorbi and Singh-Amaranath, 1973; Harrison and Smith, 1973; Reynolds and Moslen, 1974; 1977).

Confirmation that there are inhalation anaesthetics with effects known as auto-induction and cross-induction is also of great interest (Van Dyke, 1966; Cohen, 1971).

However, the published studies of the enzyme induction capacity of anaesthetics vary with experimental conditions. This makes their comparison and the estimation of their true relevance to toxicity very difficult.

The studies with diethyl ether, methoxyflurane, halothane, fluroxene and isoflurane seem to prove the hepatic microsomal hydroxylase enzyme induction capacity of these substances, although in a non-uniform way. For example, diethyl ether acts as an inducer of the phenobarbitone type, increasing the components of the microsomal electron transport system (cytochrome P-450; NADPH-dependent reductase of cytochrome *c*; and cytochrome *b*5) and stimulates the metabolism of substrates of type I (hexobarbitone and

TABLE II. *Effect of exposure to different concentrations of enflurane for different times, on ratio of liver to body weight and on microsomal protein as a proportion of liver or body weight. No change was statistically significant*

Duration of exposure (days)	$\frac{\text{Liver weight (g)}}{\text{body weight (g)}} \times 100$	Microsomal protein (mg per g liver)	Microsomal protein (µg per 100 g body weight)
Enflurane 1%			
Control	4.084 ± 0.527 ($n = 7$)	8.177 ± 0.672 ($n = 7$)	33.346 ± 3.765 ($n = 7$)
3	4.113 ± 0.141 ($n = 8$)	8.600 ± 0.742 ($n = 8$)	35.758 ± 3.851 ($n = 8$)
Control	3.989 ± 0.277 ($n = 6$)	10.026 ± 0.446 ($n = 6$)	40.863 ± 1.945 ($n = 6$)
7	4.310 ± 0.348 ($n = 4$)	8.998 ± 0.751 ($n = 4$)	38.704 ± 4.537 ($n = 4$)
10	3.806 ± 0.285 ($n = 4$)	8.479 ± 0.270 ($n = 4$)	32.065 ± 1.636 ($n = 4$)
14	4.211 ± 0.135 ($n = 4$)	9.547 ± 0.655 ($n = 4$)	39.979 ± 1.816 ($n = 4$)
17	4.006 ± 0.135 ($n = 4$)	9.419 ± 0.871 ($n = 4$)	37.413 ± 2.434 ($n = 4$)
21	4.540 ± 0.208 ($n = 4$)	7.817 ± 0.206 ($n = 4$)	35.614 ± 2.540 ($n = 4$)
24	3.748 ± 0.102 ($n = 4$)	7.970 ± 1.767 ($n = 4$)	29.367 ± 5.235 ($n = 4$)
Enflurane 2%			
Control	4.084 ± 0.527 ($n = 7$)	8.177 ± 0.672 ($n = 7$)	33.346 ± 3.765 ($n = 7$)
3	4.109 ± 0.139 ($n = 8$)	8.968 ± 0.801 ($n = 6$)	37.279 ± 4.159 ($n = 8$)
Control	3.989 ± 0.152 ($n = 7$)	9.238 ± 0.563 ($n = 7$)	36.684 ± 2.209 ($n = 7$)
7	4.225 ± 0.281 ($n = 4$)	10.743 ± 0.826 ($n = 4$)	44.972 ± 2.756 ($n = 4$)
10	4.340 ± 1.042 ($n = 4$)	9.557 ± 1.309 ($n = 4$)	40.857 ± 4.185 ($n = 4$)
14	4.515 ± 0.157 ($n = 4$)	8.831 ± 0.257 ($n = 4$)	39.894 ± 4.533 ($n = 4$)
17	4.514 ± 0.198 ($n = 4$)	9.020 ± 0.622 ($n = 4$)	40.377 ± 1.591 ($n = 4$)
21	3.943 ± 0.081 ($n = 4$)	9.568 ± 0.460 ($n = 4$)	37.793 ± 1.511 ($n = 4$)
24	4.241 ± 0.158 ($n = 4$)	9.309 ± 0.661 ($n = 4$)	39.238 ± 1.991 ($n = 4$)
Enflurane 3%			
Control	4.084 ± 0.527 ($n = 7$)	8.177 ± 0.672 ($n = 7$)	33.346 ± 3.765 ($n = 7$)
3	4.453 ± 0.062 ($n = 4$)	9.082 ± 0.822 ($n = 4$)	40.385 ± 3.487 ($n = 4$)

aminopyrine) and of type II (aniline) (Brown and Sagalyn, 1974). There are other more selective anaesthetics since they affect only some of those processes (Brown, 1971; Davis et al., 1971; Linde and Berman, 1971; Brown and Sagalyn, 1974; Takahashi, Shigematsu and Furukawa, 1974).

Published information on the cross-induction effects of the administration of enflurane *in vivo* is scarce and incomplete. Its induction capacity has not been confirmed by direct determination of enzyme activities, such as has been performed in this study.

Our results (tables I and II) allow us to conclude that, when administered *in vivo* and under the conditions described, enflurane (1) does not show any hepatic microsomal enzyme induction capacity and does not profoundly or lastingly interfere with the microsomal protein content; (2) after a certain number of exposures varying the dose, it modifies the metabolism of aminopyrine through the isolated microsomes and inhibits it.

These results confirm the following conclusions drawn from the literature: (1) not every inhalation anaesthetic shows the same hepatic microsomal enzyme inductive capacity; (2) when present, it is not necessarily a non-specific effect; and (3) some even have inhibitory properties or properties that repress the microsomal enzyme activities. In fact, halothane and methoxyflurane, for instance, when administered *in vivo*, do not modify the metabolism of aniline (substrate type II) and they have also in common the effect of decreasing the metabolism of hexobarbitone and of ethylmorphine (substrates type I); they differ, however, in that halothane decreases the NADPH-dependent reductase activity of cythochrome *c*, while methoxyflurane increases it (Davis et al., 1971; Brown and Sagalyn, 1974).

The mechanism by which enflurane initiates the decrease of metabolism of aminopyrine (table I), has not yet been determined, and we do not think it a simple one.

If the likelihood is confirmed that enflurane in man is not an enzyme inducer, and if it is ascertained that it is not effectively an auto-inducer and does not deeply and lastingly interfere with the microsomal protein structure, then these facts, together with its apparent metabolic stability (Chase et al., 1971; Halsey et al., 1971; Cousins et al., 1976; Dooley et al., 1979), support the safety of its clinical use.

In contrast, verification of an effect that may be repressive or inhibitory of microsomal metabolic activity (the demethylation of aminopyrine) and dependent on dosage and repetition of administration, would point in another direction.

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EFFETS DE L'INHALATION D'ENFLURANE SUR LES ACTIVITES ENZYMATIQUES MICROSOMALES HEPATIQUES CHEZ LE RAT

RESUME

Nous avons fait des recherches au sujet de l'effet possible d'induction enzymatique microsomal hépatique de l'enflurane, administré par inhalation en doses anesthésiques pendant des périodes de 1 h par jour. Dans 15 groupes expérimentaux, qui différaient les uns des autres par la concentration anesthésique (1, 2 et 3% d'enflurane) et par le nombre de jours du traitement (3, 7, 10, 14, 21 et 24), nous avons vu que (1) aucune modification soit dans le rapport du poids du foie au poids du corps soit dans le contenu protéinique microsomal ne s'était produite; (2) aucune modification de l'activité de l'hydroxylase de l'aniline n'avait eu lieu; (3) une diminution de l'activité de déméthylase de l'aminopyrine s'opérait après un certain nombre d'expositions variant avec la dose.

AUSWIRKUNGEN DER EINATMUNG VON ENFLURAN AUF DIE LEBERMIKROSOMAL ENZYMAKTIVITÄTEN IN DER RATTE

ZUSAMMENFASSUNG

Wir untersuchten die möglichen Auswirkungen einer Enfluran-Einatmung in narkotischen Dosen über einen Zeitraum von 1 Stunde pro Tag auf die Leber-Mikrosomalenzyminduktion. Bei 15 durch verschiedene Narkosekonzentrationen von einander unterschiedlichen Gruppen (1, 2 und 3% Enfluran), die jeweils 3, 7, 10, 14, 21 und 24 Tage behandelt wurden, stellten wir fest: (1) keine Veränderungen im Leber/Körpergewichtverhältnis oder im mikrosomalen Proteingehalt; (2) keine Modifikationen der Anilinhydroxylase-Aktivität; (3) eine absinkende Aminopyrindemethylase-Aktivität nach mehreren Einwirkungen der Droge, je nach Dosis.

EFECTOS DE LA INHALACION DEL ENFLURANO SOBRE LAS ACTIVIDADES ENZIMATICAS MICROSOMALES HEPATICAS EN EL RATON

SUMARIO

Hemos investigado el posible efecto de inducción enzimática microsomal hepática del enflurano, administrado por inhalación en dosis anestéticas por periodos de 1 h al día. En 15 grupos experimentales que diferían el uno del otro por la concentración anestética (1, 2 y 3% de enflurano) y por el número de días de tratamiento (3, 7, 10, 14, 21 y 24), encontramos (1) ninguna alteración ya sea en la relación del hígado para con el peso del cuerpo ni tampoco en el contenido proteínico microsomal; (2) ninguna modificación de la actividad de hidroxilasa de la anilina; (3) una disminución de la actividad de demetilasa de la aminopirina después de un cierto número de exposiciones, que variaba según la dosis.

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EFFECTS OF HALOTHANE AND SODIUM NITROPRUSSIDE ON RENAL FUNCTION AND AUTOREGULATION

A. OHMURA, K. C. WONG, N. L. PACE AND R. K. JOHANSEN

SUMMARY

The effects of sodium nitroprusside and halothane on renal autoregulation and kidney function were studied in 14 mongrel dogs at mean arterial pressures of 120, 100, 80, 60 and 40 mm Hg. In group 1, stepwise decreases in mean arterial pressure were achieved by increasing the halothane concentration. In group II, mean arterial pressure was decreased by infusing sodium nitroprusside during halothane anaesthesia. In group I, renal blood flow decreased significantly at mean arterial pressures of 100, 80, 60 and 40 mm Hg. In group II, renal blood flow was well maintained at mean arterial pressures of 100 and 80 mm Hg, but decreased significantly at 60 and 40 mm Hg; at these low pressures flow was greater in group II than in group I. There were no significant differences between two groups in inulin clearance, inulin clearance/renal plasma flow, urine output, urine osmolarity and sodium excretion rate. Significantly larger fractions of cardiac output were distributed to the kidneys in group I.

Sodium-nitroprusside (SNP) is used widely to induce hypotension during anaesthesia, its rapid onset and short duration of action producing hypotension easily and permitting adequate control (Tinker and Michenfelder, 1976). That such hypotension may compromise renal function and cause renal failure after operation is still of concern (Larson, 1964). Bastron and Kaloyanides (1972) provided evidence that SNP-induced hypotension caused significant decreases in the function of the intact kidney. However, no comparison of renal function was made between hypotension induced with SNP and hypotension produced by other methods. Leighton, Bruce and MacLeod (1977) demonstrated that at mean arterial pressures (m.a.p.) of 50–60 mm Hg induced by SNP, renal blood flow (RBF) decreased significantly but returned to control in 12 min in the intact kidney. They suggested that hypotension induced with SNP may provide significant protection of the kidney. However, they did not study other aspects of renal function. The present study compared renal function and autoregulation in dogs during hypotension, induced by increasing concentrations of halothane, with that produced by the infusion of SNP during halothane anaesthesia.

METHODS

Two groups of seven mongrel dogs weighing 17–24 kg were anaesthetized with thiopentone 25 mg kg^{-1} i.v. The trachea was intubated and the lungs ventilated artificially with 0.9% halothane expired concentration in 50% nitrogen and 50% oxygen. Arterial blood-gas tensions were assessed frequently; pH and $P\text{CO}_2$ were maintained between 7.37 and 7.43 units and 31 and 37 mm Hg, respectively. End-tidal halothane concentration was monitored with a Beckman infra-red halothane analyser. Two foreleg veins were catheterized. One thousand millilitre of isotonic saline was infused over 50–70 min during the surgical preparation. The kidney, left renal vessels and ureter were exposed through a left subcostal incision. An appropriate pre-calibrated electromagnetic flow probe was placed around the left renal artery, and was connected to a Statham Blood Flow Meter (Model SP2201 with non-occlusive zero). The ureter was catheterized to permit timed collections of urine. All visible renal nerves were severed, and the renal artery was swabbed with 70% alcohol. The left femoral artery was cannulated to permit monitoring of arterial pressure and blood sampling. Loose snares were placed around both carotid arteries and were tightened when necessary to increase

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systemic arterial pressure to 120 mm Hg. A pulmonary artery catheter incorporating a thermistor was floated into the pulmonary artery from a jugular vein. Pulmonary artery temperature was monitored and maintained between 37 and 39 °C by placing the dog on a heating pad. Dogs were kept in the supine position throughout the study. Following the surgical preparation a priming dose of inulin (7.5 ml of 10% solution) was given, followed by a continuous 10-ml min^{-1} infusion of isotonic normal saline containing a maintenance dose of inulin (20 ml of 10% solution in 1000 ml of isotonic saline). A 15-min stabilization period was allowed before control data were obtained at m.a.p. 120 mm Hg (adjusted by carotid constriction). M.a.p. values were then decreased sequential in both groups in 20-mm Hg steps from 120 mm Hg to 40 mm Hg. In group I m.a.p. was decreased by increasing the inspired halothane concentration; in group II SNP 50 mg in 250 ml of 50% dextrose in water was infused while the administration of halothane was continued. M.a.p. was not returned to control between each step decrease. At each value of m.a.p. 15 min was allowed for stabilization and then a 10-min urine collection was obtained; RBF was measured at the midpoint of urine collection after the non-occlusive zero had been tested. A femoral artery blood sample was taken at the midpoint of the urine collection. Urine sodium concentration was determined with a flame photometer (Instrumentation Lab., Inc., Lexington, Mass.). Plasma and urine inulin concentrations were determined by spectrophotometry and inulin clearance calculated with reference to 100 g kidney weight. Renal plasma flow (RPF) was derived from RBF (1 − Hct $litre^{-1}$). After the study was completed, the kidney was isolated, trimmed and weighed. Comparison of measured and derived variables between the treatment groups was made by a profile analysis technique using a multivariate analysis of variance method. Individual comparisons were performed by paired and non-paired Student *t* tests. $P < 0.05$ was considered statistically significant. Data were expressed as mean ± SEM.

RESULTS

Following the control measurement at m.a.p. 120 mm Hg, the mean times to complete the studies were 120 ± 6 min and 110 ± 4 min in groups I and II, respectively. Arterial pH and P_{CO_2} values at m.a.p. 120 mm Hg and 40 mm Hg are presented in table I: there was no acid–base imbalance at any m.a.p. in either group. RBF,

TABLE I. *Arterial blood–gas tensions and mean arterial pressure in the dog (mean ± SEM, n = 7). BE = base excess*

	120 mm Hg			40 mm Hg		
	pH (unit)	P_{CO_2} (kPa)	BE (mmol)	pH (unit)	P_{CO_2} (kPa)	BE (mmol)
Group I	7.39 ±0.01	34 ±1	−3.1 ±0.3	7.42 ±0.01	32 ±1	−2.0 ±0.2
Group II	7.40 ±0.01	35 ±1	−3.8 ±0.3	7.39 ±0.01	34 ±1	−2.8 +0.3

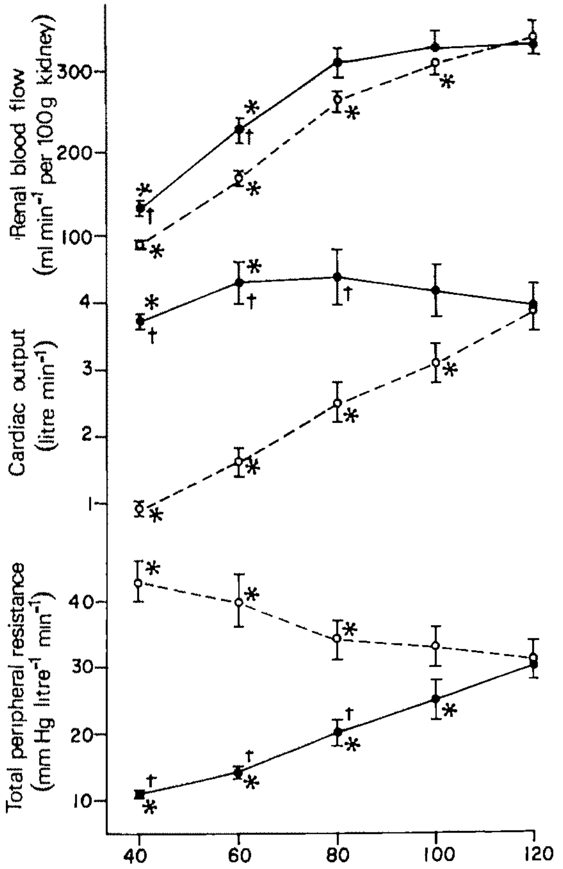

FIG. 1. Changes in renal blood flow, cardiac output and total peripheral resistance with decrease in mean arterial pressure. - - - = group I (hypotension with halothane); ——— = group II (hypotension with sodium nitroprusside). Mean ± SEM; $n = 7$. *$P < 0.05$ different from control values; †$P < 0.05$ difference between group I and group II.

TABLE II. *Changes in kidney function with stepwise decreases in mean arterial pressure in the dog (mean ± SEM, $n = 7$), Cl_{in} = Inulin clearance; FF = filtration fraction.* *$P < 0.05$ *significant change from control*

MAP (mm Hg)	Group	Cl_{in}	FF	Urine output (ml min^{-1})	Sodium Excretion (µmol min^{-1})	Urine osmol
120	I	57±5	0.28±0.04	2.79±0.17	385±20	431±37
	II	61±5	0.29±0.04	3.01±0.50	403±67	408±66
100	I	49±2	0.25±0.02	2.50±0.15*	336±20*	515±68*
	II	56±6	0.30±0.05	2.68±0.41*	363±57*	510±63*
80	I	40±1*	0.26±0.03	1.13±0.09*	163±14*	636±69*
	II	46±5*	0.22±0.05	1.00±0.16*	153±14*	624±67*
60	I	17±2*	0.15±0.03*	0.19±0.01*	23±2*	730±56*
	II	18±2*	0.09±0.04*	0.07±0.01*	10±2*	772±90*

cardiac output and total peripheral resistance (TPR) are depicted in figure 1. Inulin clearance (Cl_{in}), filtration fraction (FF = Cl_{in}/RPF), urine output, sodium excretion rate and urine osmolarity are summarized in table II.

In group I the mean end-tidal halothane concentrations were 0.9% ± 0.0, 1.14% ± 0.02, 1.35% ± 0.04, 1.51% ± 0.06 and 1.76% ± 0.05 at m.a.p. 120, 100, 80, 60 and 40 mm Hg, respectively. In group II the mean rate of SNP infusion was 20 ± 1.1 µg kg^{-1} min^{-1} and total doses did not exceed 1.4 mg kg^{-1} h^{-1} in any animal.

In group I RBF decreased significantly ($P < 0.05$) from control at m.a.p. 100–40 mm Hg. In group II RBF was significantly decreased at m.a.p. 60 and 40 mm Hg only. When the overall responses of RBF were compared (group mean test), the difference between the two groups was statistically significant ($P = 0.0001$).

In group I cardiac output decreased significantly ($P < 0.05$) from 3.9 ± 0.3 litre min^{-1} at m.a.p. 120 mm Hg to 0.9 ± 0.1 litre min^{-1} at m.a.p. 40 mm Hg. TPR increased progressively and was significantly greater ($P < 0.05$) than control at m.a.p. 80, 60 and 40 mm Hg. In group II cardiac output was well maintained and it was slightly greater ($P < 0.05$) at m.a.p. 60 mm Hg and slightly less ($P < 0.05$) at m.a.p. 40 mm Hg than the control value. TPR in group II decreased progressively and these values at smaller m.a.p. were significantly different ($P < 0.05$) from control. The group mean test showed statistically significant differences in cardiac output ($P = 0.0001$) and TPR ($P = 0.0001$) between the groups. RBF as a fraction of cardiac output (RBF/cardiac output) is shown in figure 2. In group I this value was well maintained and at m.a.p. 80 and 60 mm Hg was significantly greater than control ($P < 0.05$). In group II it decreased steadily to become significantly less than control at m.a.p. 80, 60 and 40 mm Hg. The overall RBF/cardiac output responses were statistically different ($P = 0.003$) between the two groups.

Cl_{in} did not decrease significantly in either group at m.a.p. 100 mm Hg and the values at 80 and 60 mm Hg were significantly less than control ($P < 0.05$). FF was well maintained at 100 and 80 mm Hg and then decreased significantly

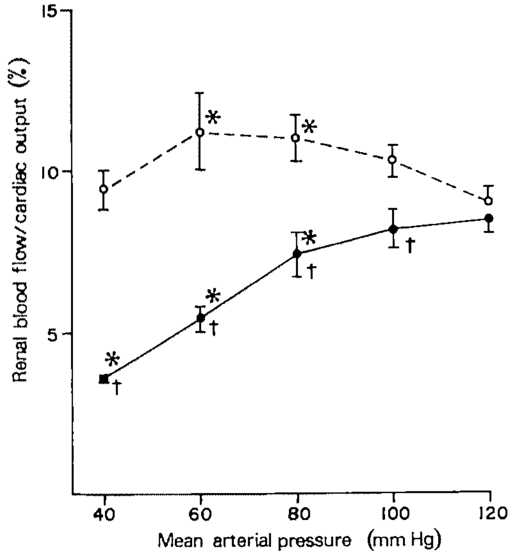

FIG. 2. Changes in renal blood flow as a fraction of cardiac output with decreases in mean arterial pressure. - - - = group I (hypotension with halothane); —— = group II (hypotension with sodium nitroprusside). Mean ± SEM, $n = 7$. *$P < 0.05$ different from control values; †$P < 0.05$ difference between group I and group II.

($P < 0.05$) at m.a.p. 60 mm Hg in both groups.

Urine osmolarity increased in both groups as m.a.p. was reduced. Data at m.a.p. 40 mm Hg are not available because urine samples were unobtainable. Urine output and sodium excretion rate in both groups were significantly less than control at m.a.p. 100, 80 and 60 mm Hg ($P < 0.05$). There were no significant differences in Cl_{in}, FF, urine output, sodium excretion rate and urine osmolarity between the two groups.

DISCUSSION

The purpose of this study was to compare renal function and autoregulation during two hypotensive techniques: the infusion of SNP and deep halothane anaesthesia. Halothane was chosen because it is a widely used anaesthetic agent and has been used to induce controlled hypotension. Despite the marked hypotension with SNP and halothane, tissue oxygenation and normal pH and base excess were maintained; thus severe acid–base imbalance was not the cause of the changes in renal function in our study.

SNP produced hypotension by decreasing TPR while maintaining relatively constant cardiac output. Halothane decreased m.a.p. by decreasing cardiac output, while TPR was increased during hypotension (fig. 1). RBF in the SNP group was unaltered with the decrease in m.a.p. to 80 mm Hg, but showed significant reductions at 60 and 40 mm Hg. In the halothane group compromised RBF was demonstrated with a decrease in m.a.p. from 120 to 100 mm Hg and is compatible with the report of Deutsh and colleagues (1966) in man. Under the present experimental conditions, Cl_{in}, FF, urine output, sodium excretion rate and urine osmolarity were not significantly different between the groups.

If SNP had a protective action on the kidney, hypotension induced with SNP would be expected to cause less impairment of function, especially when RBF was maintained. Unfortunately our results did not support this thesis. Contrary to the findings of Leighton, Bruce and MacLeod (1977) RBF did not return to control after 25 min of hypotension with SNP at any of the smaller m.a.p. values. However, the following differences in the experimental design between ours and Leighton's study need to considered. Their animals were allowed to recover for at least 4 days after surgery. Although halothane was chosen as an anaesthetic in both studies, the duration of hypotension in our study was significantly longer because of the stepwise decrease in m.a.p. and multiple measurements. Bagshaw, Cox and Campbell (1977) also observed a significant decrease in RBF when m.a.p. was reduced by 55% or more of the control value with an infusion of SNP under 1 MAC halothane anaesthesia. They did not describe the duration of hypotension before RBF was measured.

Although Bastron and Kaloyanides (1972) concluded that SNP does not provide protection to a kidney at lower m.a.p., no comparison was made of renal function between hypotension induced by SNP and other methods. Such comparisons were made in our study and substantiate their conclusion.

It is known that moderate hypotension induced with SNP releases renin in a kidney (Miller et al., 1977). It is also known that the renin–angiotensin system does redistribute RBF from the outer cortex to the inner cortex and medulla. Carrier and Friborg (1969) showed that the vasoconstrictive response in the outer cortex to angiotension infusion was much more severe than that in the inner cortex. Sein and colleagues (1971) observed a similar redistribution of RBF from the outer cortex to the inner cortex in dogs during the intrarenal administration of vasodilators such as acetylcholine or bradykinin. This might explain why urine output and the rate of sodium excretion decreased significantly at m.a.p. 100 and 80 mm Hg despite a constant RBF (SNP animals) since the long-loop juxtamedullary nephrons, predominantly distributed in the inner cortex and medulla, are more capable of retaining salt and water than the short-loop outer cortical nephrons (Barger and Herd, 1971).

The response of the sympathetic nervous system is also important in the distribution of intrarenal blood flow. Although sympathetic fibres were severed and swabbed with alcohol, the release of circulating catecholamines in response to hypotension was not totally excluded and could decrease the blood flow in the outer cortex more profoundly than that in the inner cortex (Hollenberg et al., 1968).

RBF at m.a.p. 100 and 80 mm Hg decreased significantly from the control value in the halothane group, when hypotension was induced by increasing inspiratory halothane concentration. Leighton, Koth and Wenkstern (1973), using a similar method, obtained a similar result with methoxyflurane. Bastron, Perkins and Pyne (1977) concluded that halothane did not abolish renal autoregulation, based on the observation in isolated kidneys in which renal perfusion pressure was decreased by raising kidney position relative to the heart; end-tidal halothane concentration was maintained at 0.9%. Our results are not in disagreement with the latter observation. The SNP group was anaesthetized with halothane 0.9% in a steady state, during infusion of SNP. The minimal basal halothane concentration did not alter RBF at m.a.p. of 100 and 80 mm Hg. The results suggest a dose-related response in the detrimental effect of halothane on renal autoregulation.

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EFFECTS DE L'HALOTHANE ET DU NITROPRUSSIATE DE SODIUM SUR LA FONCTION ET L'AUTOREGULATION RENALES

RESUME

Les effets qu'ont le nitroprussiate de sodium et l'halothane sur l'autorégulation rénale et sur la fonction des reins ont été étudiés sur 14 chiens bâtards à des pressions artérielles moyennes de 120, 100, 80, 60 et 40 mm Hg. Dans le groupe I, nous avons obtenu des diminutions échelonnées de la pression artérielle moyenne en augmentant la concentration d'halothane. Dans le groupe II, nous avons fait baisser la pression artérielle moyenne en faisant une perfusion de nitroprussiate de sodium pendant l'anesthésie à l'halothane. Dans le groupe I, le débit sanguin rénal a diminué d'une manière significative aux pressions artérielles moyennes de 100, 80, 60 et 40 mm Hg. Dans le groupe II, le débit sanguin rénal a été maintenu aux pressions artérielles moyennes de 100 et de 80 mm Hg, mais il a baissé d'une manière significative à 60 et 40 mm Hg; à ces basses pressions, le débit a été plus important dans less groupe II que dans le groupe I. Il n'y a pas eu de différence importante entre ces deux groupes, en ce qui concerne l'élimination de l'inuline, l'élimination de l'inuline et le débit de plasma rénal, la production d'urine, l'osmolarité de l'urine et le taux d'excrétion du sodium. Ce qui a été significatif dans le groupe I, c'est que des fractions plus grandes de débit cardiaque ont été distribuées aux reins.

DIE AUSWIRKUNGEN VON HALOTHAN UND NITROPRUSSIDNATRIUM AUF FUNKTION UND SELBSTREGELUNG DER NIEREN

ZUSAMMENFASSUNG

Die Auswirkungen von Nitroprussidnatrium und Halothan auf die Selbstregelung und Funktion der Nieren von 14 Bastardhunden wurden bei mittleren Arteriendrücken von 120, 100, 80, 60 und 40 mm Hg studiert. Bei der ersten gruppe wurde eine schrittweise Reduzierung des mittleren Arteriendruckes durch Steigerrung der Halothankonzentration erreicht. Bei der zweiten gruppe wurde der mittlere Arteriendruck durch Infusion von Nitroprussidnatrium während der Halothannarkose reduziert. Bei der ersten gruppe nahm der Nierenblutkreislauf bei mittleren Arteriendrücken von 100, 80, 60 und 40 mm Hg bedeutend ab. Bei der zweiten gruppe hielt sich der Blutkreislauf bei mittleren Arteriendrücken von 100, und 80 mm Hg, nahm aber bei 60 und 40 mm Hg bedeutend ab. Bei diesen niedrigen Drücken war Nieren-kreislauf bei der zweiten gruppe grösser als bei der ersten. Es ergaben sich keine bedeutende Unterschiede zwischen den beiden Gruppen in Bezug auf Inulinclearance, Inulinclearance/Nierenplasmafluss, Urinproduktion, Urinosmolarität und Natriumausscheidungsgeschwindigkeit. Bei der ersten gruppe wurden bedeutend grössere Teile des Herzausstossvolumens an die Nieren geleitet.

Br. J. Anaesth. (1982), 54, 109

CORRESPONDENCE

MALPOSITION OF A CENTRAL VENOUS CATHETER

Sir,—A 40-year-old man underwent mitral valve replacement, followed 4 months later by a further mitral valve replacement for infective endocarditis of the prosthesis; 6 weeks after the second operation, he developed septicaemic shock. As no peripheral veins were palpable a 13.3-cm 16-gauge Angiocath (Deseret Pharmaceuticals) was introduced via the left internal jugular vein using a low approach. After entry to the vein it proved impossible to advance the catheter so a flexible guide wire was introduced and the catheter passed easily down the vein. Oscillation responding to respiration was observed, but fast fluctuation synchronous with the pulse was not seen and aspiration of blood by syringe was less easy than normal. A diluted potassium chloride infusion caused immediate severe left shoulder tip pain which ceased on discontinuing the infusion and recurred on recommencing it. The introduction of contrast medium to the catheter (fig.1) showed the tip (arrowed) filling the left pericardiophrenic veins.

The complications of central venous cannulation are those directly attributable to the insertion, those resulting from the presence of an indwelling catheter and those resulting from catheter malposition. Malposition is least likely when the internal jugular approach has been used, but approximately 5% will not lie within the superior vena cava or the right atrium (Malatinsky et al., 1976). Malposition in a persistent left superior vena cava, the azygos, internal thoracic, subclavian, axillary and hepatic veins, the inferior vena cava, the right ventricle and pulmonary artery have been reported but we believe that malposition in the pericardiophrenic veins has not been recorded.

The guide wire directed the catheter across the left brachiocephalic vein into the left superior intercostal vein and then down to the termination of the left pericardiophrenic veins. We feel that the use of a guide wire may have contributed to the malposition. A shorter cannula would not have reached this position but may not have been long enough to lie within the superior vena cava or right atrium.

We assume that the shoulder tip pain was caused by irritation of the hemidiaphragm by retrograde perfusion with the potassium chloride solution. Unusual complaints following insertion of a central venous catheter should raise the possibility of malposition as, for example, the "ear-gurgling sign" (Gilner, 1977) when the catheter tip lay near the middle ear.

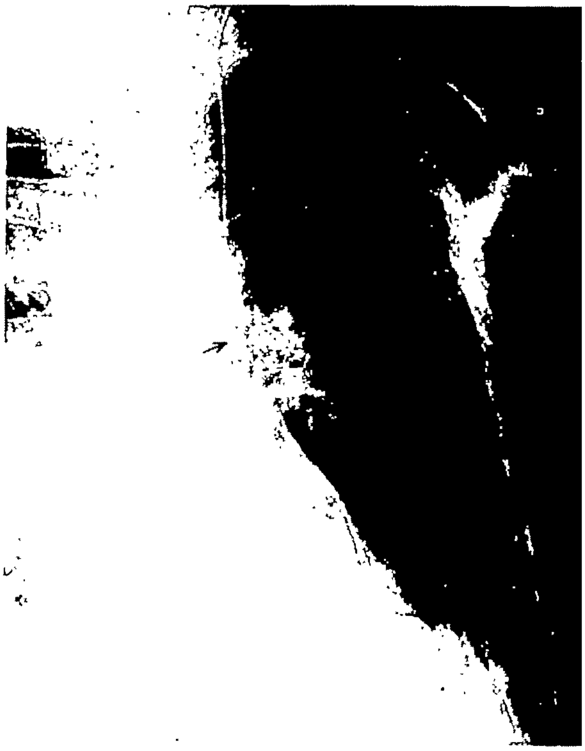

FIG. 1. Chest x-ray with contrast in catheter (tip arrowed).

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PANCURONIUM AND NODAL RHYTHM

Sir,—We read with interest the letter by Saemund and Dalenius (1981) on the occurrence of nodal rhythm related to the injection of pancuronium. Our studies on the haemodynamic responses to antagonism of neuromuscular block have revealed a significantly greater frequency of nodal rhythm in patients receiving pancuronium compared with tubocurarine or alcuronium. This rhythm disturbance is associated with bradycardia during the reversal of pancuronium block.

We have studied healthy patients undergoing minor surgery under anaesthesia comprising thiopentone, nitrous oxide and an analgesic drug (Heinonen and Takkunen, 1977; Heinonen, Salmenperä and Takkunen, 1981 and in preparation). After surgery, the 90% block was antagonized with neostigmine $0.03\%\,\text{mg kg}^{-1}$ preceded by atropine $0.015\,\text{mg kg}^{-1}$. A temporary nodal rhythm after neostigmine was observed in 15 of 41 pancuronium-treated patients, whereas all the patients treated with tubocurarine ($n = 15$) or alcuronium ($n = 22$) maintained sinus rhythm (pancuronium *v.* tubocurarine or alcuronium, $P<0.01$; Chi-square-test).

Saemund and Dalenius reported five cases of nodal rhythm directly related to the injection of pancuronium 0.1 mg kg^{-1}. We, too, have witnessed several examples of transient nodal rhythm after the administration of pancuronium and not infrequently this rhythm disturbance has been accompanied by a decrease in arterial pressure. Recent reviews (Prys-Roberts, 1981) emphasize the potential deleterious effects of this rhythm disturbance in patients suffering from hypertension and coronary artery heart disease and we have demonstrated severe deterioration of circulation during an episode of nodal rhythm even in an apparently healthy patient (Heinonen, Salmenperä and Takkunen, 1981a). Although atrioventricular dissociation has been observed in a considerable proportion of cases during the onset of alcuronium block also (Haldemann and Schaer, 1972), a re-evaluation of the frequency of nodal rhythm in association with various neuromuscular blocking drugs may be indicated.

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ANTAGONISM OF KETAMINE BY 4-AMINOPYRIDINE AND PHYSOSTIGMINE

Sir,—I have read with interest the correspondence from Tung, Figallo and Brandom (1981) and Ruprecht (1981), regarding 4-aminopyridine (4-AP) reversal of ketamine–diazepam anaesthesia. I entirely agree with Tung's statement that "the efficacy of 4-aminopyridine in antagonizing the anaesthetic effect of ketamine may be because of the antagonistic effects on prejunctional acetylcholine release in the c.n.s. in a manner similar to that in motor nerve terminals", and I may add, from my own research on the effect of 4-AP on *Maccacus rhesus* monkeys (Martinez-Aguirre and Crul, 1979) and from other unpublished data, it is tempting to postulate that 4-AP might additionally displace ketamine from its c.n.s. receptors by competing with it. This may be a result of their structure–activity relationship, causing a sudden, brief, increase in plasma ketamine concentration, as opposed to the control series.

With respect to Ruprecht's comments that "no reliable treatment has been suggested for 4-AP overdose", I would like to recall that 4-AP is a known convulsant drug at doses greater than 1.0 mg kg^{-1} i.v. Our previous work on 4-AP (Martínez-Aguirre, 1980; Martínez-Aguirre, Kaufman and Paz-Alvarez, 1980; Martínez-Aguirre, Wikinski and Bravo, 1980) indicates that 4-AP is an effective reversal agent for ketamine–diazepam anaesthesia in children, 0.3 mg kg^{-1} i.v. being the least active dose, and 1.0 mg kg^{-1} i.v. the most active dose. This latter dose has been shown to produce fine muscle tremors or movements in some patients, so that our recommended dose for reversal of ketamine–benzodiazepam anaesthesia is 0.6 mg kg^{-1} i.v. We have observed two cases of inadvertent overdose of 4-AP (1.2 and 1.7 mg kg^{-1} i.v., respectively), with the occurrence of generalized convulsions, which began with spasms of the facial muscles. They were quickly prevented by the i.v. administration of diazepam 0.2 mg kg^{-1} in one patient and of midazolam (Ro 21-3981) 0.15 mg kg^{-1} in the other; both patients received oxygen via a face mask. At no time was there evidence of acute respiratory insufficiency.

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POSITIVE END-EXPIRATORY PRESSURE AND AIR EMBOLISM IN THE SITTING POSITION

Sir,—We read with interest the paper by Campkin (1981) on posture and ventilation during posterior fossa and cervical operations and agree with the author's view of the benefits of controlled hyperventilation and the sitting position. Hewer and Logue (1962) and Lee, Lichtmann and Weintraub (1981) advocated the use of positive end-expiratory pressure (PEEP) to reduce the frequency of air embolism. We wish to report our experience on the use of PEEP to prevent air embolism.

Since 1978 we have used PEEP up to 10 cm H_2O in 169 patients, in the sitting position, undergoing infratentorial and cervical surgery. There was accurate monitoring of the heart rate, systemic arterial pressure and e.c.g., with a catheter in the right atrium for the measurement of central venous pressure, and precordial ultrasonic Doppler transducer. Only one case of air embolism, from a puncture wound of the pin-type head holder device, was detected at the end of the procedure when

PEEP was discontinued at the time of closure of the surgical wound (Cabezudo et al., 1981).

In our experience this degree of PEEP in the sitting position produces negligible changes in intracranial pressure and in arterial pressure.

We think it is a useful method to prevent air entry to the vascular compartment, and is superior to intermittent manual compression of the jugular veins at the root of the neck.

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A FOLEY CATHETER INTRODUCER FOR ENDOTRACHEAL TUBES

Sir,—An introducer made from a stiffened 18-gauge Foley catheter has proved an easy and atraumatic aid to inserting armoured endotracheal tubes, which are modified by cutting their bevelled ends straight across. The special merits of the device are first, the balloon of the catheter is used to grip the tube, so that tube and introducer become a single unit, and second, the terminal 10 cm are very flexible, allowing easy straightening after entry to the trachea, and making blind and semi-blind tracheal introduction simple. When used routinely, it has almost eliminated minor intubation difficulties.

Two copper wires of domestic mains cable type are used: 40 cm of 2-mm wire, and 50 cm of 1-mm (fig. 1). Both are sandpapered smooth at the tip, and the thinner wire is bent back by about 3 mm to make a blunt tip. The wires are inserted to the catheter, the distal end of the longer, thinner wire extending 10 cm beyond the tip of the thicker wire. In the 18 gauge catheter these make a firm fit (fig. 2). The catheter is placed in the tube with one half of the balloon protruding from the end. The balloon is inflated with air to grip the tube and form a smooth end profile (fig. 3). If lubricant is used to aid withdrawal (unnecessary in new tubes), the balloon must remain free of it. The introducer and tube may be bent to any suitable curve for introduction. The balloon is then deflated, and the introducer withdrawn.

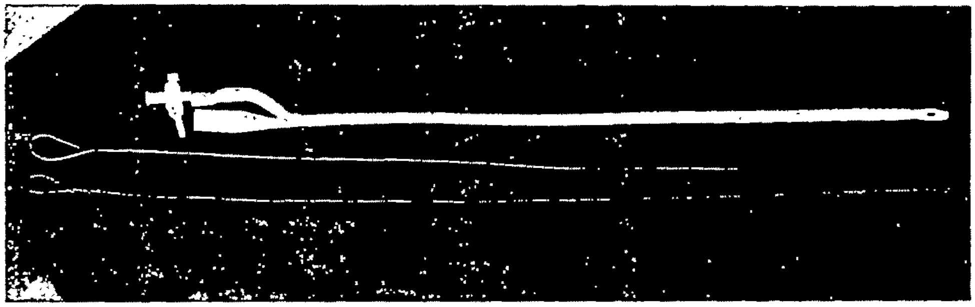

FIG. 1. The introducer components before assembly.

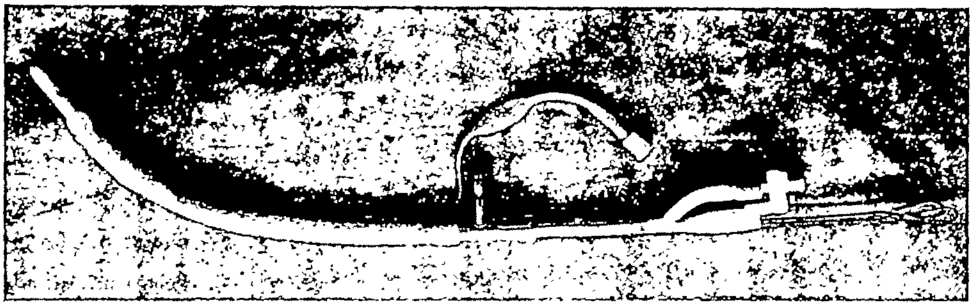

FIG 2. The introducer in a 9.5-mm armoured tube ready for use.

Although as described the introducer cannot be used with tubes smaller than 7.0 mm diameter smaller versions could readily be devised. The principle seems greatly superior to the "railroading" method commonly used.

T. A. BOLISTON
Taunton

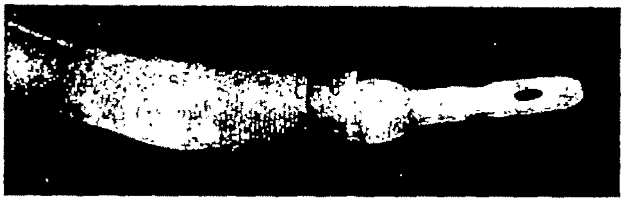

FIG. 3. Distal end of the tube with the introducer in position.

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UNDER THE INFLUENCE

A History of Nitrous Oxide and Oxygen Anaesthesia

W. D. A. SMITH

Reader in Anaesthesia, University of Leeds and Honorary Consultant Anaesthetist,
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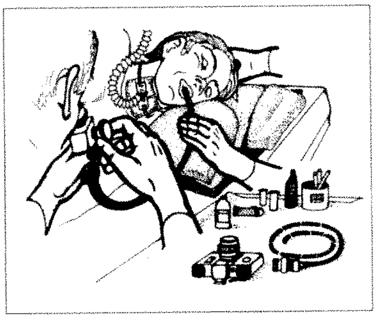

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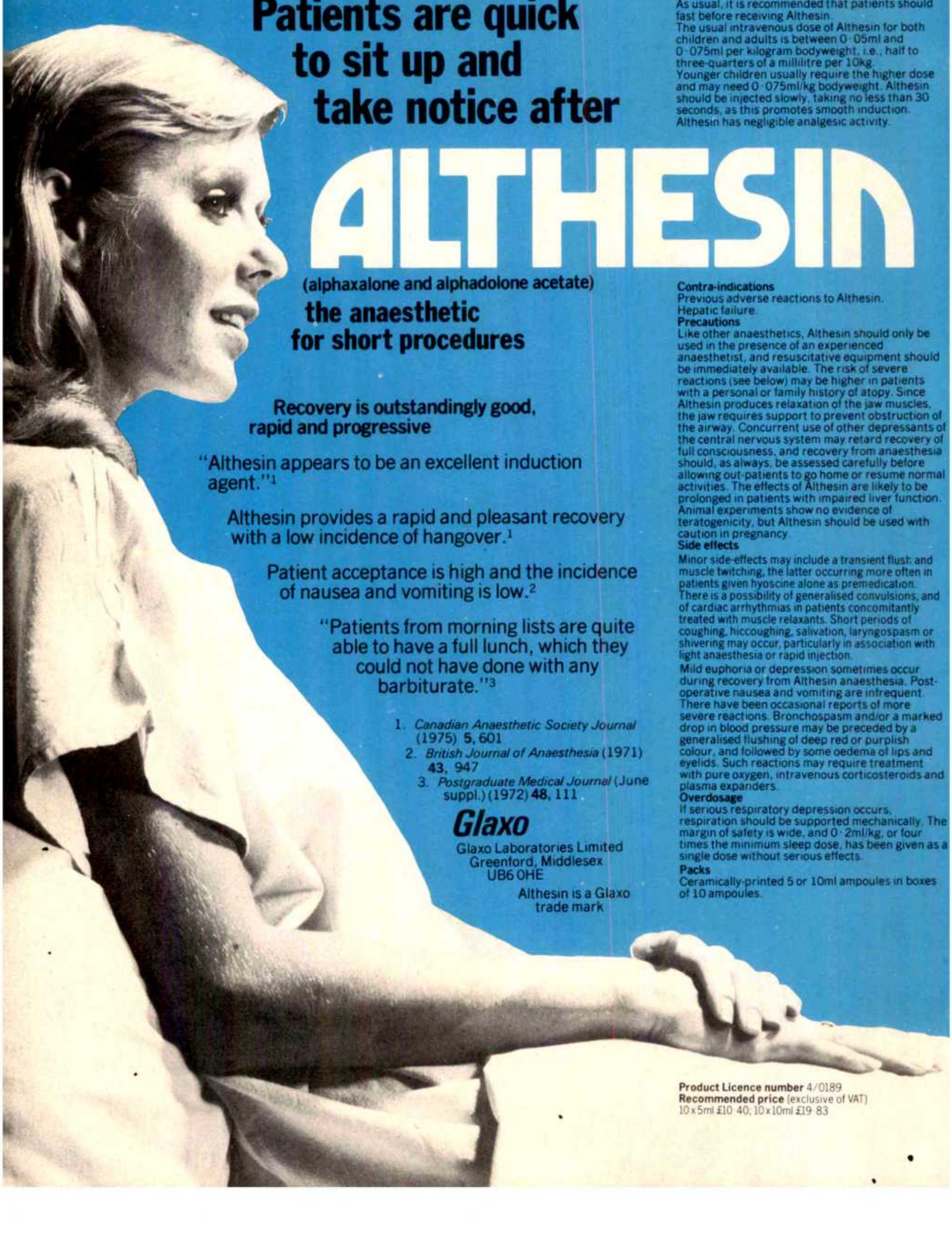

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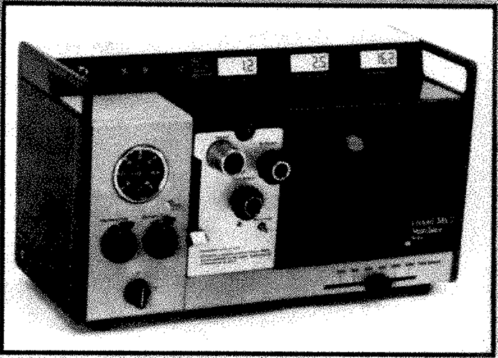

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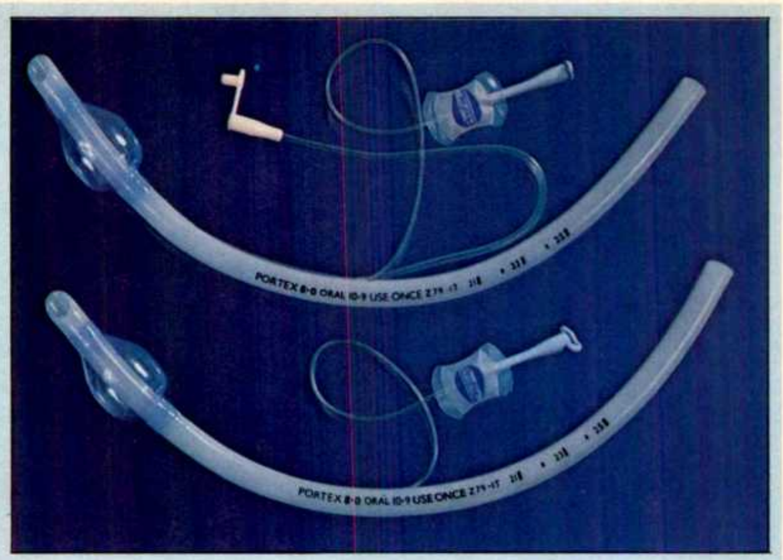

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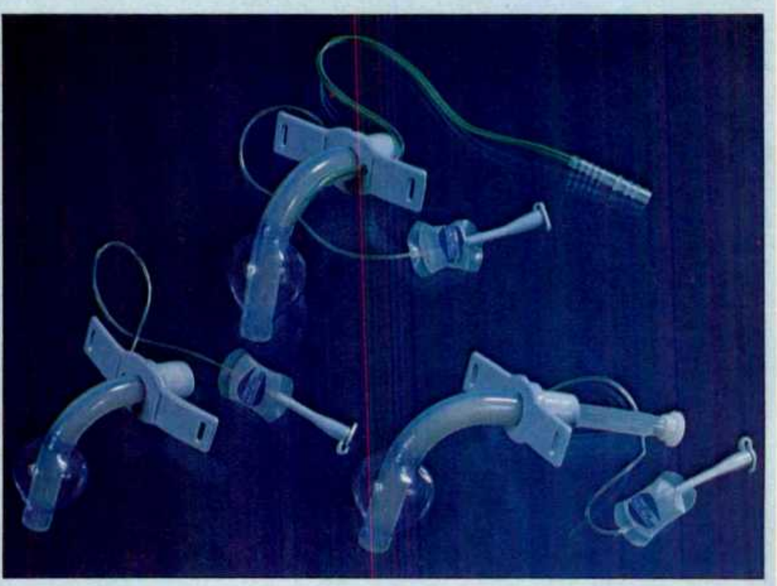

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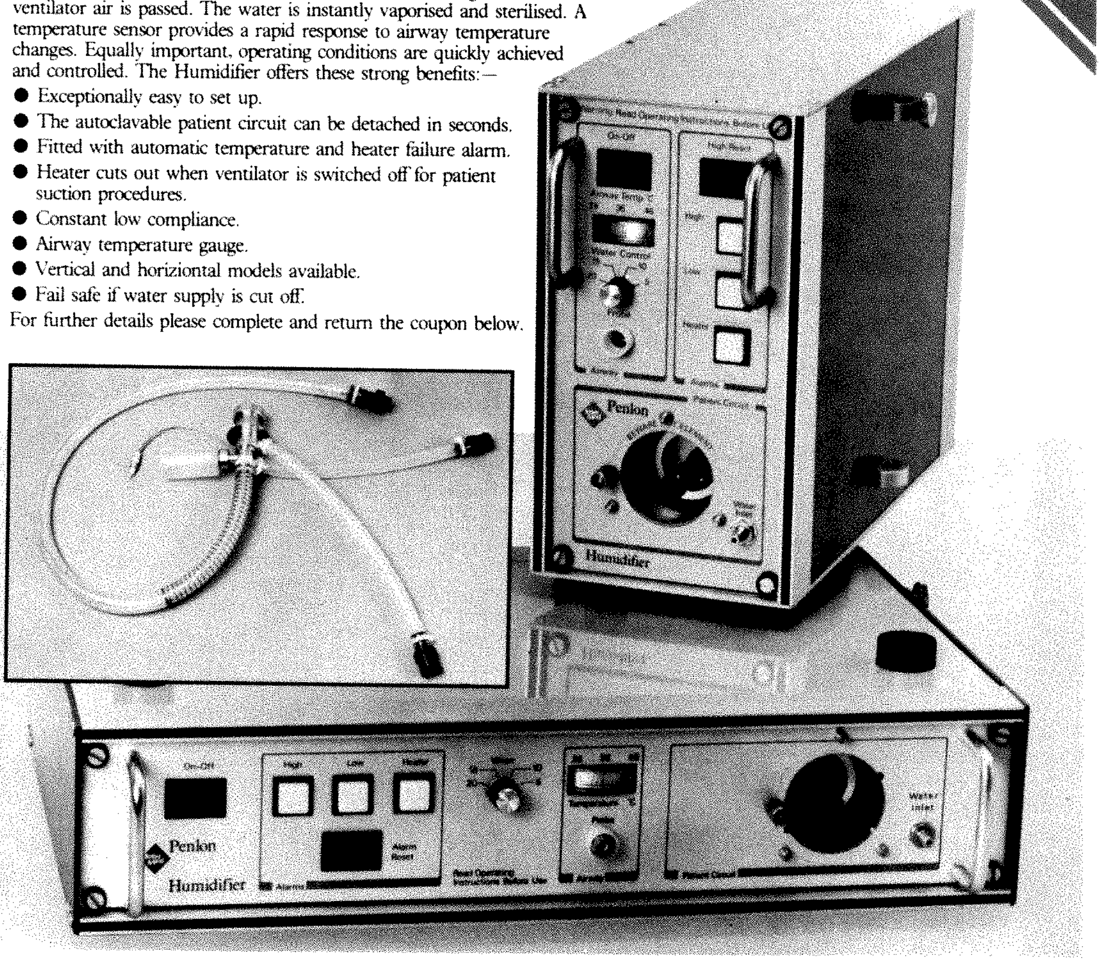

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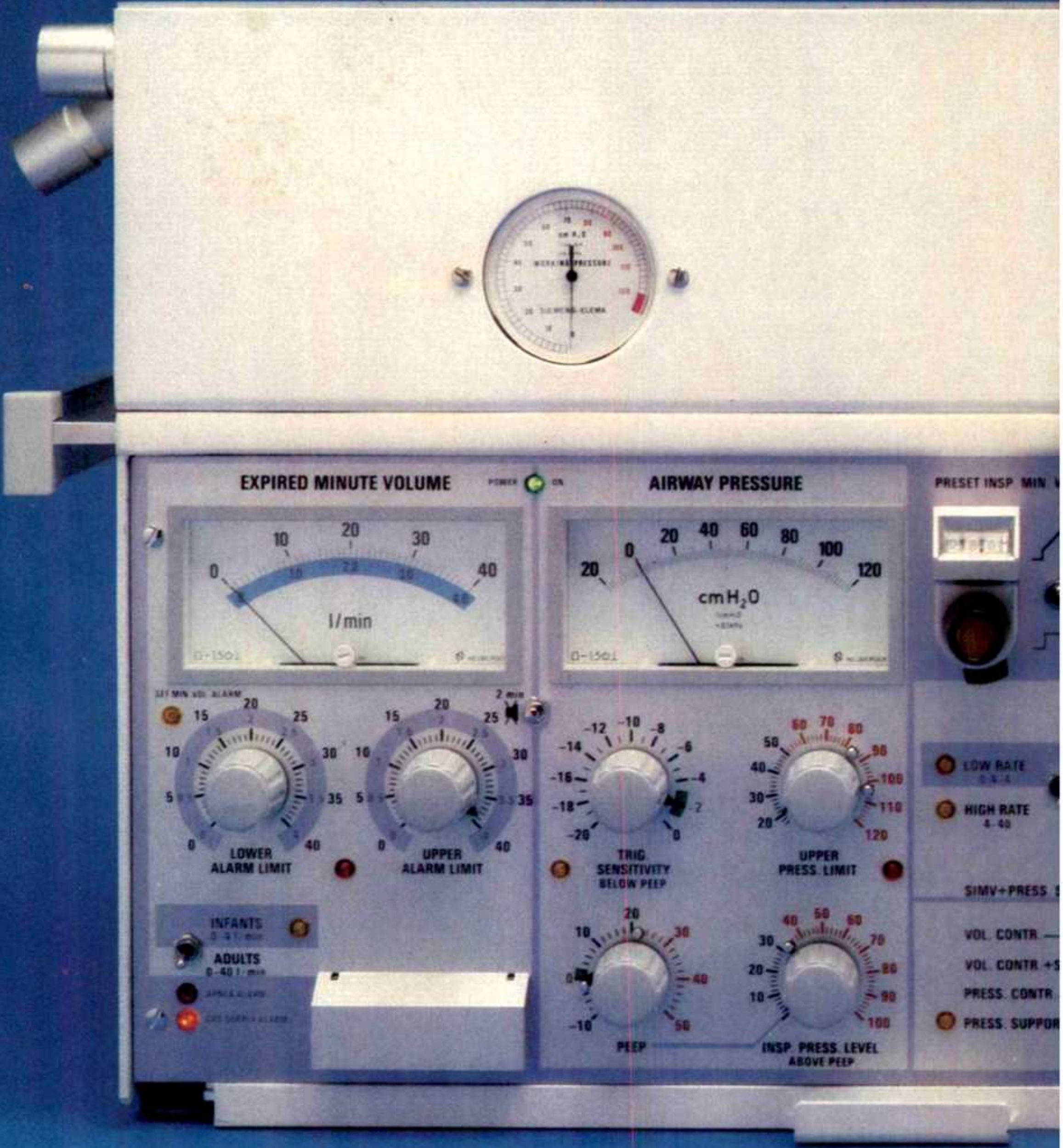

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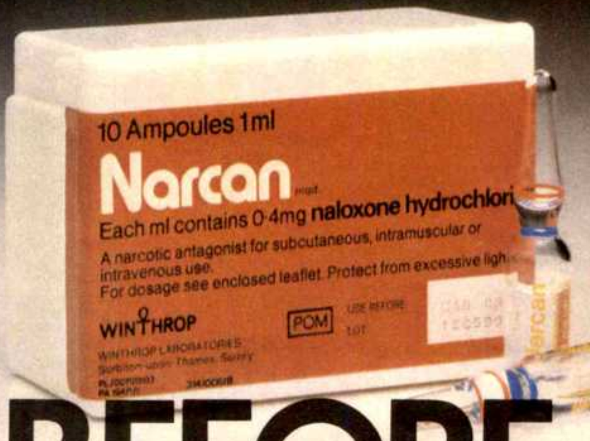
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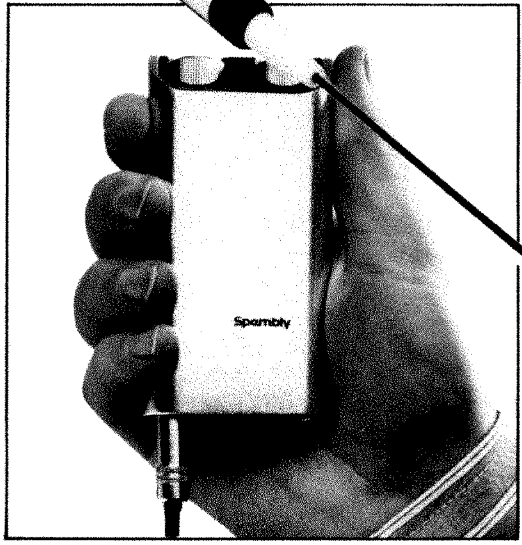

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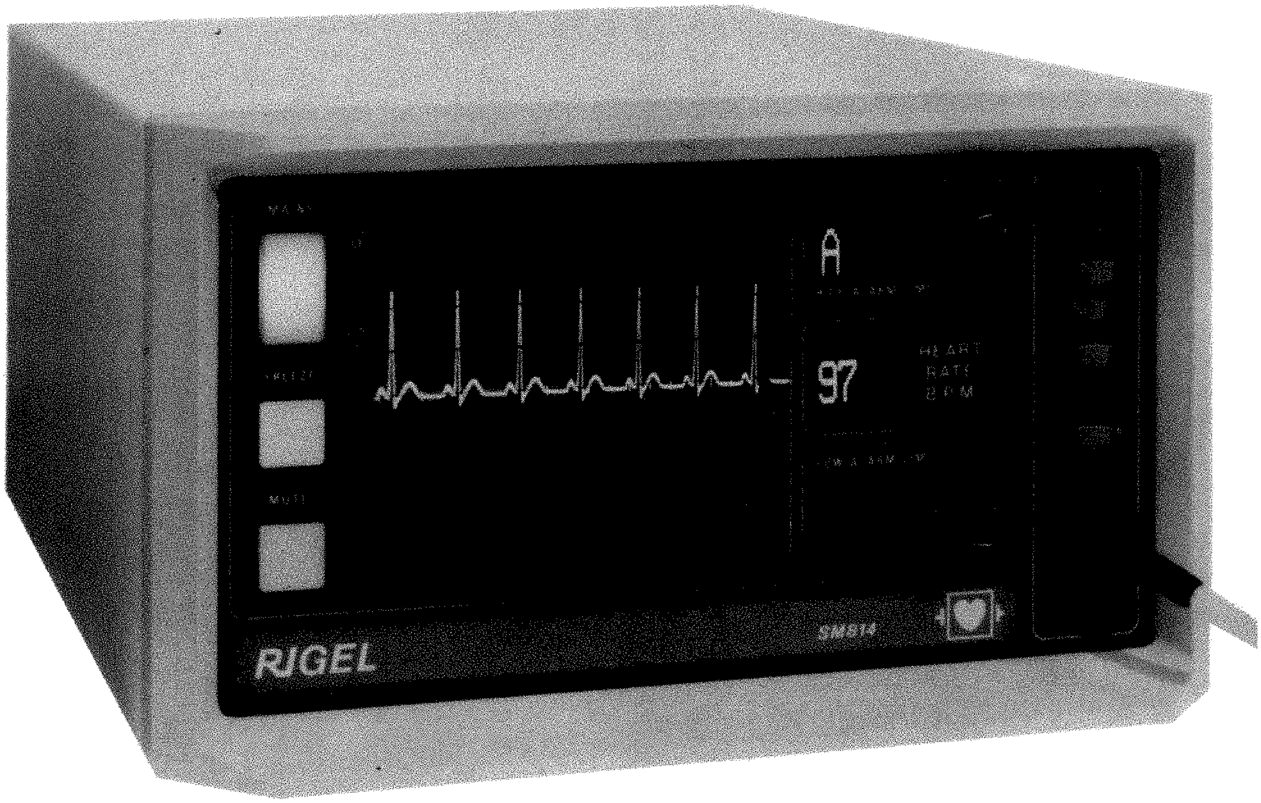

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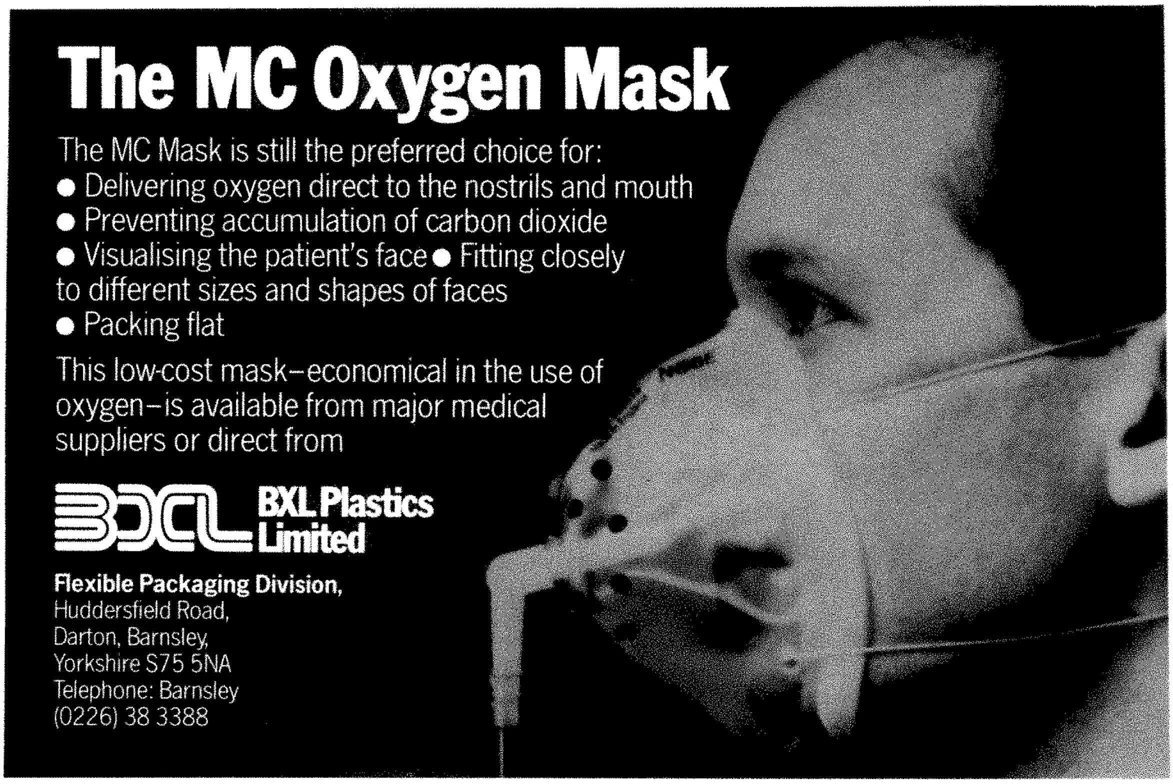

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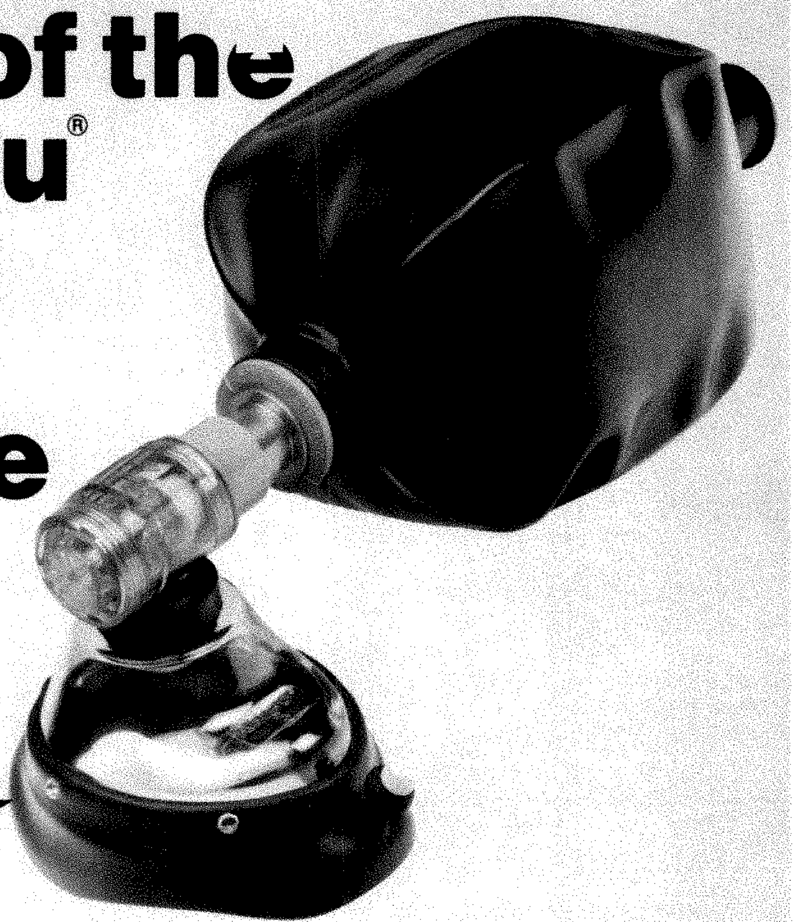

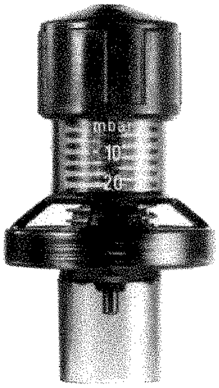

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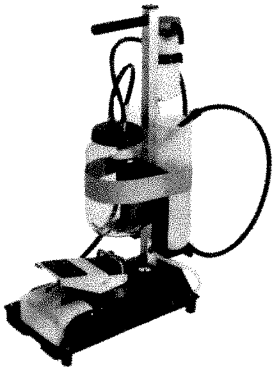

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EDITORIAL

NEUROMUSCULAR BLOCKADE

Anaesthetists can use neuromuscular blocking drugs to facilitate endotracheal intubation and to produce relaxation of muscles, permitting easy surgical access without too much thought as to what is happening at the neuromuscular junction and as to what factors govern the extent and duration of the actions producing paralysis. Provided that patients are ventilated adequately problems are rare, but they do occur and Harrison (1978) attributed 10 of his series of 53 deaths to which anaesthesia contributed to myoneural block leading to respiratory inadequacy. This issue of the journal is designed to review recent work describing what happens at the junction when various drugs are given, what factors govern the rates at which the various actions appear and disappear and how neuromuscular block can be monitored clinically.

The traditional view of the drugs used by anaesthetists is that non-depolarizing drugs compete with acetylcholine for the receptors. At high concentrations insufficient amounts of acetylcholine are present to produce depolarization. Thus this type of block can be surmounted using acetylcholinesterase inhibitors. Clinically, partial non-depolarizing block is recognized by a weak twitch response, tetanic fade and post-tetanic twitch facilitation. In contrast, drugs such as suxamethonium produce paralysis by depolarizing the postsynaptic membrane and making it unexcitable by acetycholine. Neostigmine makes the block worse. Clinically partial block is associated with a weak twitch response, no fade of tetanic response and no post-tetanic potentiation. The introduction of "train-of-four" testing (Ali, Utting and Gray, 1971) shows patterns of response with the two classes of drugs which are similar to the tetanic responses. It has always been tempting to assume that the patterns of response seen clinically are a result of the two mechanisms of competition and depolarization, but this is not so; prolonged use of suxamethonium leads to a pattern of response much like that seen with tubocurarine, and yet neostigmine will not always antagonize such a block. Standaert (1982) describes here the work looking at events in the nerve terminal, whilst Dreyer (1982) assesses the state of knowledge about the acetylcholine receptor. He reviews work showing that some drugs may be causing neuromuscular block at the junction, not by acting at the acetylcholine receptor, but at the next stage. They may block the channels in the membrane normally opened when acetylcholine interacts with the receptors. Anaesthetists will need to consider whether some of the prolonged and unusual blocks seen in patients are a result of presynaptic or postsynaptic processes. Interactions with the large number of differing drugs given to anaesthetized patients may be producing our problems.

Age and disease alter the rates at which the body will distribute, metabolize and eliminate neuromuscular blocking drugs. Assay techniques are now available for many of our agents and it is becoming easier to predict when unusual intensities and durations of actions may be expected. Thus with most of our current armamentarium we can expect that renal failure will delay elimination and might prolong action. Obstructive jaundice can have the same effect. Miller (1982) and Cronnelly and Morris (1982) review these pharmacokinetic considerations for neuromuscular blocking drugs and their antagonists.

The relationship between plasma drug concentrations and clinical effects are complex, especially when considering the usual clinical administration of blockers by intermittent i.v. bolus doses. Although some dispute exists as to the value of matching pharmacokinetics and effects, Hull (1982) shows how these two aspects can be brought together.

Despite the debate as to what is the value of these new clinical sciences, there is no dispute that continuous monitoring of the extent of neuromuscular block is extremely valuable in assessing when further doses of drug are needed and when antagonism can be expected to produce rapid or slow reversal of paralysis. Monitoring is especially valuable in the elderly, the sick and those in whom many drugs are given. Personal experience shows that a standard dose of pancuronium ($0.1\,mg\,kg^{-1}$) can produce an effect lasting between 20 and 120 min. Few would undertake major surgery without adequate monitoring of the cardiovascular state; peripheral nerve stimulators have much to commend them. Viby-Mogensen (1982) reviews how neuromuscular block can be assessed.

What of the future? In 1975 Savarese and Kitz suggested that three sorts of new agents were needed: a short-acting agent producing complete paralysis for only 10 min, a medium agent producing paralysis for 20–30 min and a long-acting agent lasting more than an hour. All should be non-depolarizing drugs. In 1981 Savarese stated that drugs of the second and third types were then available. Org NC45 (vecuronium) Norman and Bowman, 1980), atracurium (Hughes and Chapple, 1981; Payne and Hughes, 1981) and BWA444U (Savarese et al., 1981) all produce non-depolarizing block of a duration shorter than those of equipotent doses of pancuronium. Recovery is rapid. In contrast, pipecurium is a long-acting agent (Karpati and Biro, 1980). All new drugs are screened to ensure that unwanted side-effects are not present with doses likely to be used by clinicians. Bowman (1982) in this issue reviews these actions and the testing programme needed to demonstrate them.

The new short-acting drugs look extremely impressive but, when they are introduced, some care will be needed and some modifications of current practice will be possible. A rapid recovery may not be desirable, especially in the middle of an operation. Monitoring by peripheral nerve stimulation will eliminate this problem, but with a rapid recovery it may well be that continuous infusion techniques will become popular. If we maintain anaesthesia by continuous inhalations of vapour or infusions of other drugs it seems logical to go the same way with neuromuscular block.

Finally we still need a replacement for suxamethonium. Durant and Katz (1982) almost imply they are writing its obituary. Yet despite its many limitations and contraindications few of us at the moment could manage without it. Is the pursuit of its replacement like the search for the Holy Grail?

John Norman

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ACETYLCHOLINE RECEPTOR

F. DREYER

The main processes of neuromuscular transmission have been known for about 10 years (Katz, 1966, 1969). The presynaptic mechanisms were particularly well studied compared with the agonist–receptor interaction on the postsynaptic membrane. During the past 10 years this has changed considerably as a result of the development of new techniques in morphology, biochemistry and especially electrophysiology, so that now the acetylcholine receptor (ACh-R) is the best known membrane-bound receptor protein.

The technique of interference optics makes possible visualization of the motor end-plates, facilitating many morphological and electrophysiological experiments. Freeze-fracture and freeze-etching techniques have brought a much better view of the ultrastructure of the pre- and postsynaptic membrane. With immunohistochemical and autoradiographic electron microscopy, the exact localization and the density of ACh-R in the postsynaptic membrane could be established. Biochemists succeeded in isolating and characterizing the receptor protein. Antibodies against the ACh-R could be produced, and they induced an experimental myasthenia in animals. Electrophysiology provided several sophisticated methods to measure the interaction of drug molecules with the ACh-R on a molecular level.

The purpose of this article is to discuss and illustrate on a more basic level these last methods and their results, because they have provided the greatest insight into the molecular interaction of drugs with the ACh-receptors. It is not my intention to give an exhaustive coverage of the literature. Those who want a deeper insight into other, often more complex, problems are referred to several reviews published on this field in recent years (Rang, 1975; Gage, 1976; Ginsborg and Jenkinson, 1976; Steinbach and Stevens, 1976; Neher and Stevens, 1977; Landau, 1978; Barrantes, 1979; Colquhoun, 1979; Stevens, 1980; Wray, 1980; Adams, 1981; Colquhoun, 1981).

LOCALIZATION OF ACETYLCHOLINE RECEPTORS

For some electrophysiological and morphological methods it is of great advantage to identify the neuromuscular junction visually. This is possible with the Nomarski-interference optics introduced by McMahan and Kuffler (1971). Figure 1 shows examples of living motor end–plates of frog and mammals. In the frog the unmyelinated nerve terminal is elongated, with several branches for hundreds of microns. Synaptic transmission occurs over the whole length of the nerve terminal. The mammalian neuromuscular junction is relatively compact and extends about 10 µm above the muscle membrane, justifying the name "end-plate". As revealed by ionophoretic application of agonists, the ACh-R are mainly restricted to this end-plate region in normal muscles.

Thin section electron microscopy, and especially the relatively new freeze-fracture and freeze-etching techniques, have allowed investigation of the three-dimensional ultrastructure of the pre- and postsynaptic membrane. Figure 2 shows schematically a part of the neuromuscular junction of the frog (which has mostly been studied because of its regular structure). The presynaptic membrane is characterized by specialized structures, called "active zones", which are believed to be the release sites of the ACh-filled vesicles. These "active zones" are located just opposite the openings of the junctional folds.

An important step in the characterization of ACh-R properties was the finding of the snake venom α-bungarotoxin (α-BuTx), a polypeptide which binds specifically and almost irreversibly to nicotinic receptors on skeletal muscles (Lee, 1972). This toxin competes with cholinergic agonists and antagonists for the same binding sites on ACh-R. Using radionuclide- or peroxidase-labelled α-BuTx, it could be shown by elec-

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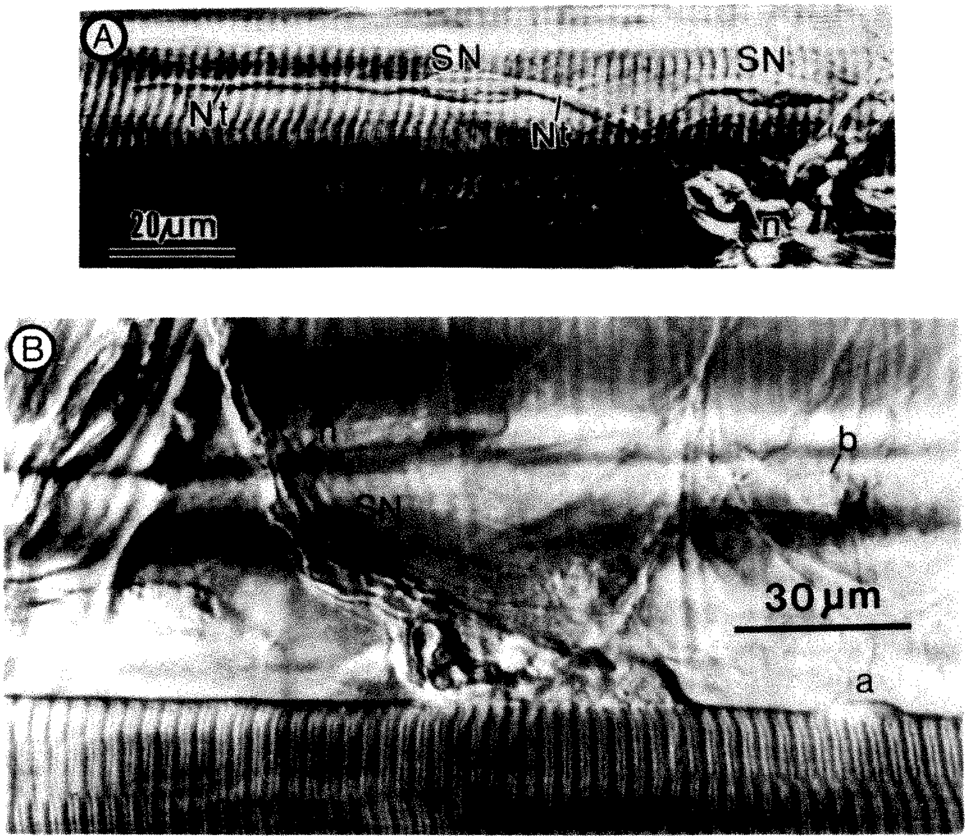

FIG. 1. Living motor end-plates viewed in the Nomarski-interference microscope. A: Frog neuromuscular junction of the M. cutaneus pectoris (reproduced from Peper et al., 1974, with permission). B: Side view of a guineapig motor end-plate of the M. sternocleidomastoideus, pars clavicularis. n = myelinated nerve fibre with node of Ranvier; Nt = nerve terminal; SN = Schwann cell nuclei; a = muscle nucleus; b = collagen nucleus (reproduced from Dreyer et al., 1976, with permission).

tron microscopy that the ACh-R are sharply localized to the crests of the junctional folds just beneath the active zones (fig. 2; Fertuck and Salpeter, 1974; Daniels and Vogel, 1975). The number of α-BuTx binding sites was estimated to about $30\,000\ \mu\mathrm{m}^{-2}$ at these areas (Fertuck and Salpeter, 1976). With the freeze-etching method particles of about 10 nm diameter and of a density of approximately $7500\ \mu\mathrm{m}^{-2}$ were found exactly at the same location (Dreyer et al., 1973; Peper et al., 1974). Most probably these particles represent the receptor proteins. The lower value of the particle density compared with the α-BuTx binding site density can be explained by the fact that two to four α-BuTx molecules bind to one Ach-R. The particle density is in good agreement with the number of ACh-activated channels which can be opened at high acetylcholine concentrations (Dreyer and Peper, 1975). The old view that the physiological role of the junctional folds is to increase the subsynaptic receptive membrane area had to be abandoned. On the other hand the specific acetylcholinesterase, which destroys the transmitter in the synaptic cleft, is mainly located in the basement membrane and evenly distributed over the whole subsynaptic membrane including the depths of the folds.

On normal muscle fibres the ACh-R density decreases markedly outside the end-plate area, being about 1000-fold less in extrasynaptic membrane more than 200 µm away from the end-plate. However, in developing or denervated muscles ACh-receptors, called extrajunctional ACh-R, exist over the entire muscle membrane. Their properties differ in some respect from those in the synaptic membrane and their density depends

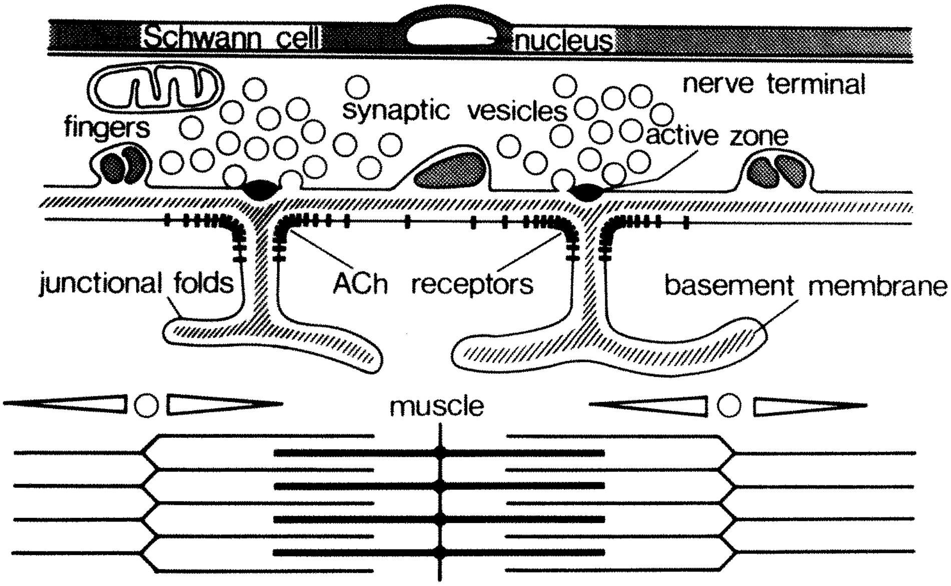

FIG. 2. Schematic drawing of the ultrastructure of the frog neuromuscular junction in longitudinal section. Thin fingers from a Schwann cell, overlaying the nerve terminal, often completely embrace the nerve terminal in regions between the junctional folds, thus dividing the terminal into compartments. Numerous synaptic vesicles often congregate near specialized presynaptic structures, called "active zones". These are located just opposite the openings of the junctional folds. Synaptic vesicles fuse at the active zones. ACh-receptors are located in a high density mainly at the crests of the junctional folds. The distance between the folds is about 1 μm. The same structures are found in mammalian motor end-plates, but their arrangement is not as regular as in the frog neuromuscular junction.

strongly on a neural trophic factor (for review see Fambrough, 1979).

BIOCHEMISTRY OF THE ACETYLCHOLINE RECEPTOR

The largest quantities of ACh-R are found in the postsynaptic membrane of the electric organs of electric fishes. Use of the snake venom α-bungarotoxin facilitated the purification and biochemical analysis of the ACh-R from these organs. The ACh-R is an integral membrane protein which extends about 5 nm into the extracellular and about 1.5 nm into the intracellular space (Ross et al., 1977). The receptor has a molecular weight of about 250 000. It consists of five glycoprotein subunits, two of them of 40 000, the others of 50 000, 60 000 and 65 000 apparent molecular weight. The 40 000 peptides carry the binding sites for both the acetylcholine and for α-BuTx (Heidmann and Changeux, 1978; Dolly, 1979). The location of the ion channel within the protein complex has not yet been identified, but recent developments in research on the receptor protein will soon provide new information about the organization of receptor subunits forming the ionophore, and about the interactions between receptors and components of their natural environment, such as the membrane lipids.

AGONIST–RECEPTOR INTERACTION

The acetylcholine receptors (ACh-R) have two functions in the physiological chain of events that leads to the contraction of muscle fibres after nerve stimulation: first, the recognition of the neurotransmitter molecules, and second, the formation of an open ion channel which results in a membrane permeability change.

A simple and often used reaction scheme which describes most of the experimental results is the following sequential reaction scheme (fig. 3):

$$nA + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} A_nR \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} A_nR^* \qquad (1)$$

After binding of n agonist molecules, A, to the n recognition sites of the receptor, R, the ion channel of which is in a shut, non-conducting conformation (resting state), the inactive agonist–receptor complex A_nR may change to an

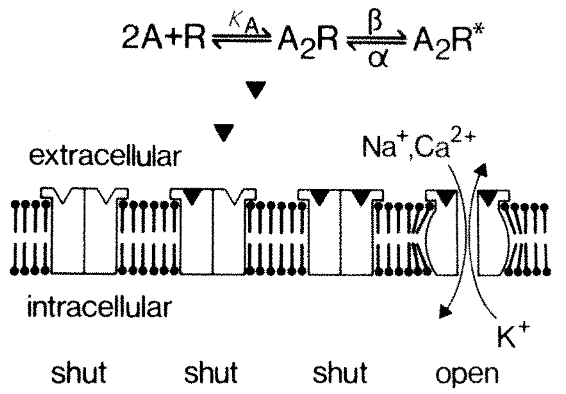
2A+R $\underset{}{\overset{K_A}{\rightleftharpoons}}$ A2R $\underset{\alpha}{\overset{\beta}{\rightleftharpoons}}$ A2R*
extracellular
Na+,Ca2+
intracellular
K+
shut
shut
shut
open

FIG. 3. Top: Reaction scheme of the interaction of an agonist like acetylcholine with an ACh-receptor. A = agonist molecules (triangles); R = ACh-receptor in its resting state; AR = agonist–receptor complex in an inactive state; AR* = agonist–receptor complex in an active state associated with an open ion channel. K_A = equilibrium constant for agonist binding; α and β = rate constants for the closing and opening reaction of the channel. Bottom: schematic illustration of the respective conformational states of the ACh-receptor with its ionophore complex in its lipid membrane environment. Two agonist molecules bind to the recognition sites in a co-operative manner to activate one ionophore complex.

active conformation $A_n R^*$. This is associated with the opening of an ion channel. The symbols α and β are the rate constants for the closing and opening mechanism and $K_A = k_{-1}/k_{+1}$ the equilibrium constant for the binding step.

The ion channel controls the flow of small cations like Na^+, K^+, and, to a lesser extent, Ca^{2+} through the membrane. The opening of the channels thus short-circuits the membrane potential, depolarizing the end-plate region of the muscle fibre. At all physiological membrane potentials Na^+ will tend to enter the cell from the extracellular space (where its concentration is high), and K^+ will tend to leave the cell from the cytoplasm. At the resting potential (or any other negative membrane potential) the net current through the ion channel flows in the inward direction. The amount of current is directly proportional to the number of open channels, so the membrane current is the most direct response of the agonist–receptor interaction which one can measure at present. For this it is necessary to keep the membrane potential constant, which can be done by the voltage-clamp technique.

The main interest today is to understand the mechanism by which the receptor complex transforms the agonist binding to the channel opening, and to know how antagonists or other drugs will influence this mechanism. For this the rate constants of the reaction steps and the elementary current through the open ion channel have to be known. There are several new biophysical techniques for the study of this drug–receptor interaction. These started with the analysis of agonist-induced membrane potential fluctuations by Katz and Miledi (1970, 1972) leading to the analysis of membrane current fluctuations (Anderson and Stevens, 1973). Then came the voltage-jump relaxation method (Adams, 1975; Neher and Sakmann, 1975; Sheridan and Lester, 1975), and finally the recording of the opening and closing of single ion channels by the "patch-clamp" method (Neher and Sakmann, 1976). In addition, quantitative ionophoresis with micropipettes allowed the complete determination of dose–response curves, up to the saturation range (Dreyer and Peper, 1975).

ELECTROPHYSIOLOGICAL METHODS OF DETERMINING ACETYLCHOLINE RECEPTOR PROPERTIES

Dose–response curve. Most experiments investigating dose–response curves from ACh-receptors yielded a sigmoidal relationship between end-plate response and agonist concentration (Katz and Thesleff, 1957; Rang, 1971; Dreyer and Peper, 1975). There are several models to explain sigmoidal curves (Colquhoun, 1973). In the co-operative model, which describes well the data of Dreyer, Peper and Sterz (1978), the binding of one agonist molecule to the receptor increases the affinity of subsequent molecules to other recognition sites of the receptor. Such co-operativity is well known from the oxygen dissociation curves of haemoglobin. It has been concluded that at least two, and possibly three or four agonist molecules have to bind to one receptor to open the ion channel with a high probability, but it cannot be excluded that, even if the probability is very low, one molecule can also activate a receptor (Dionne, Steinbach and Stevens, 1978). Such a process is not included in equation (1). With quantitative ionophoresis, complete agonist concentration–end-plate current curves can be measured which allow the determination of further important ACh-receptor properties: (1)

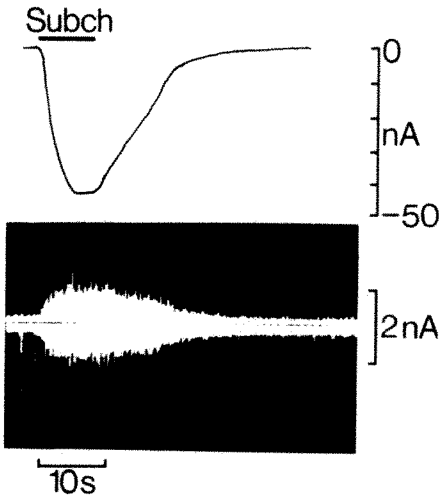

FIG. 4. Agonist-induced membrane current fluctuations in a voltage-clamped frog neuromuscular junction. The upper trace represents the voltage-clamp current at low gain. The horizontal bar indicates the application of the agonist suberyldicholine (Subch) $2\ \mu\text{mol litre}^{-1}$ by perfusion from a wide-tipped pipette placed at the end-plate. Inward current is plotted downwards according to the usual convention. The lower trace shows the same current, after passage of a high-pass filter at 0.1 Hz, on a high gain. Note the strong increase of the "noisiness" of the current during the agonist application. (Colquhoun, Dreyer and Sheridan, unpublished 1979).

the apparent dissociation constant, K, which reflects the affinity of the agonists to the ACh-R. (2) the efficacy of an agonist, one definition of which is the proportion of ion channels that can be opened at high agonist concentration. This value can be calculated from the elementary current through a single channel and the maximum current per µm length of nerve terminal which flows at high agonist concentration.

Noise analysis. A big advance in the study of drug–receptor interactions started with the finding of Katz and Miledi (1970, 1972) that the application of agonists to the ACh-receptors not only caused the well-known membrane depolarization in the end-plate area, but, in addition, an increase in the "noisiness" of the membrane potential (fig. 4). They explained these agonist-induced membrane voltage (or membrane current) fluctuations by the random opening and closing of many individual ion channels. This is illustrated in figure 5. Figure 5A shows the random opening and closing of a single channel with an elementary current, i, in the open state and zero current in the closed one. If two channels open and close independently the single currents superimpose, but still the different states can be recognized (fig. 5B). With four channels the fluctuations become larger (fig. 5C), and finally, with many activated channels, the opening and closing of individual channels can no longer be distinguished (fig. 5D). However, these agonist-induced

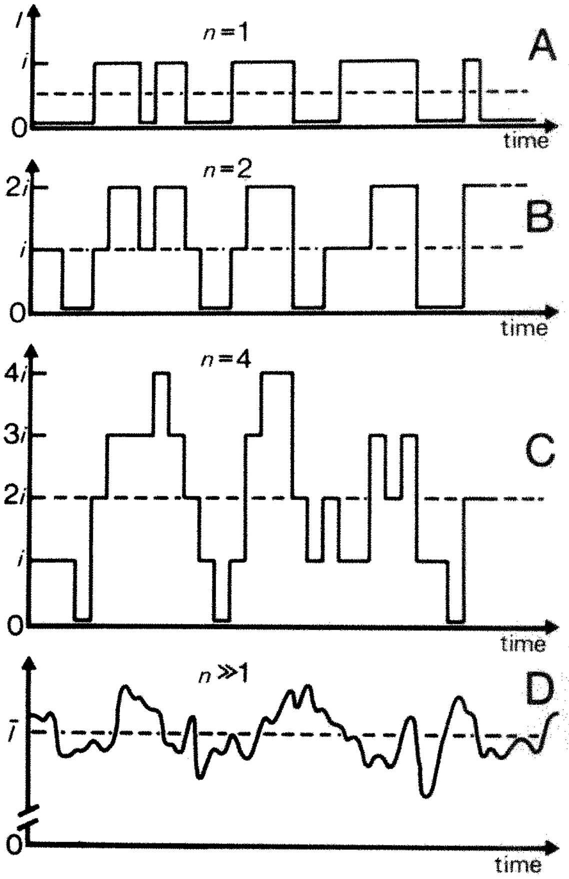

FIG. 5. Schematic illustration of the formation of agonist-induced membrane current fluctuations by the random opening and closing of ion channels. The probability of the channels being in the open or closed state is assumed to be equal. A: Opening and closing of a single, agonist-activated ion channel with an elementary current, i, during the open state. B, C, D: membrane current fluctuations caused by the superposition of two, four and of a large number of ion channels, respectively. Note the increase of the mean current, $\bar{I}$ (dashed lines) and of the fluctuations with the increasing number of activated channels. The mean current is a direct measure of the average number of open channels. From this value and the standard deviation of the noise amplitude, the elementary current through a single ion channel can be obtained. The analysis of noise frequency allows an estimate of the mean open channel lifetime.

membrane current fluctuations (figs 4, 5D) can be analysed by mathematical processes, autocorrelation function or Fourier analysis, to get information about the elementary current and the average time for which the channels stay open (reviewed by Neher and Stevens, 1977; Colquhoun, 1981). Commonly the following assumptions have been made (Anderson and Stevens, 1973): (1) the binding of the agonist molecules to the receptor is much faster than the channel opening step (which is probably not strictly true); (2) the channels exist only in the open or closed state (figs 5, 6); (3) the channels operate independently of each other. Then the fluctuation analysis yields the elementary current and a time constant:

$$\tau = \left(\alpha + \beta \cdot \frac{C_A}{C_A + K_A}\right)^{-1} \qquad (2)$$

which depends on the rate constants of the reaction given in equation (1) and on the agonist concentration, C_A. Thus, at low agonist concentration (this means only a small fraction of the available receptors is occupied) the time constant is approximately equal to $1/\alpha$, the average open channel lifetime.

Single channel currents. The most elegant method for the study of agonist–receptor interaction is to observe directly the opening and closing of individual ion channels in biological membranes. This was developed by Neher and Sakmann (1976) using a patch-clamp system for current recording from a small ($<5\,\mu m^2$) membrane area. Figure 6 shows an example. The channel opening is characterized by a step change of the current which stays constant during the open time with an amplitude of about 2.5 pA at the normal resting potential. The lifetime of each open channel will be random and therefore very variable, but the mean open time is given by $\tau = 1/\alpha$. This method has now been improved so much that, in addition to the ACh-R, many other drug- or voltage-activated channels can be directly observed (Hamill et al., 1981).

Relaxation method. A widely used method of studying drug–receptor interaction is the relaxation method. The equilibrium of the reaction (equation (1) and figure 3) can be perturbed for example by:

(a) a step-like change in membrane potential, if one of the rate constants is membrane potential-dependent (voltage-jump experiment) (Adams, 1975; Neher and Sakmann, 1975; Sheridan and Lester, 1975);

(b) a sudden change in agonist concentration following a spontaneous or nerve-evoked release of quanta of transmitter (concentration-jump experiment) (Anderson and Stevens, 1973).

Then the time-course of the concentration of one of the reactants (most conveniently for electrophysiologists, the number of open ion channels as measured by the end-plate current) is followed until a new equilibrium is established.

Figure 7A shows an example of a voltage-jump relaxation experiment. At −80 mV membrane potential and in the presence of a constant carbachol concentration (10 µmol litre^{-1}), an inward current of about −20 nA flows through the end-plate channels opened by the agonist. At time zero a jump of the membrane potential from −80 mV to −140 mV leads to an instantaneous increase of the synaptic current to about −32 nA as a result of the change in the driving force. Then with a characteristic time constant, τ, the current

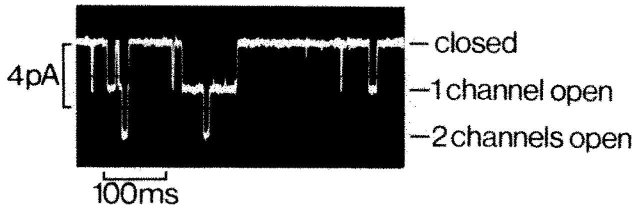

FIG. 6. Single-channel current pulses recorded with the patch-clamp method (Neher and Sakmann, 1976) from perisynaptic ACh-receptors of a normal frog muscle fibre (*Rana pipiens*) in the presence of ACh 100 nmol litre^{-1} at −90 mV membrane potential and 10 °C. The currents are shown as a downward deflection indicating an inward current. Note the constant amplitudes of the currents of 2.8 pA, but the great variability in the period of time for which the channel stays open. On average the open channel lifetime has a duration of $1/\alpha$. Further, this record demonstrates the superposition of two ACh-activated channels which are located by chance in the patch-clamp membrane area (original record kindly provided by E. Neher and B. Sakmann, Max-Planck-Institut für Biophysikalische Chemie).

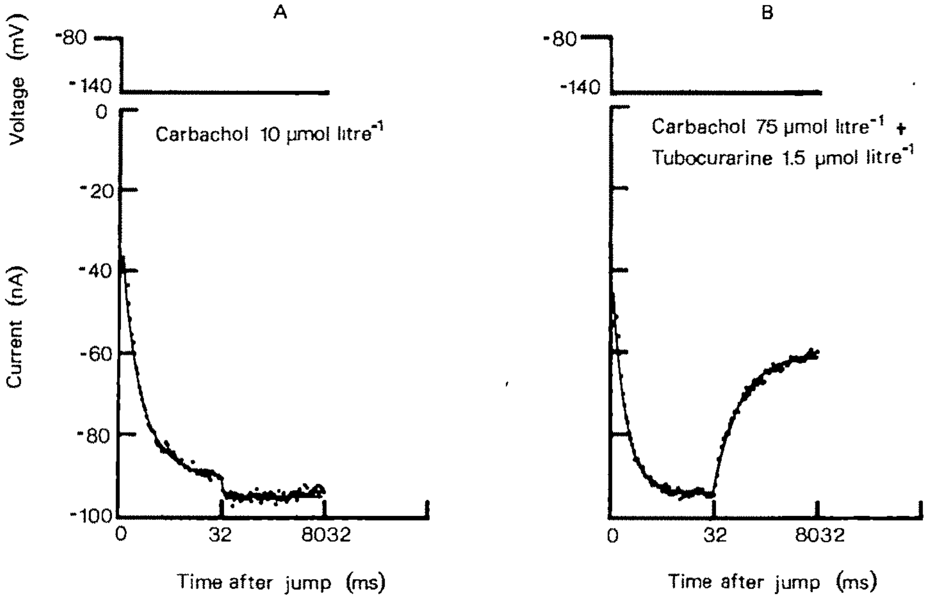

FIG. 7. Relaxation of agonist-induced end-plate current following a step change in membrane voltage from −80 mV to −140 mV (indicated at the top of each curve) in the absence (A) and presence (B) of a channel-blocking drug like tubocurarine which dissociates from the blocked channels relatively slowly. The currents were recorded for 8032 ms after the voltage change at zero time. Notice that the first 32 ms of each record is shown on a greatly expanded time scale so that the fast relaxation can be seen. In A the current could be well fitted by a single exponential curve with time constant τ of about 6.2 ms. The same voltage jump in the presence of tubocurarine 1.5 µmol litre^{-1} displays clearly two exponential components B, a fast relaxation with the time constant τ_f of about 4.3 ms which is slightly faster than the time constant τ in the absence of tubocurarine, and a slow inverse relaxation with the time constant τ_s of about 2 s in this example (reproduced from Colquhoun, Dreyer and Sheridan, 1979, with permission).

increases exponentially to a new equilibrium value, about −90 nA, because more channels open under the influence of the hyperpolarized potential. Under certain assumptions (see equation (2)) the time constant τ is a good estimate of the mean open life-time of the channels that are opened by the agonist at the new membrane potential.

The responses to ACh, released spontaneously (miniature end-plate current, m.e.p.c.) or by nerve stimulation (nerve-evoked end-plate current, e.p.c.$_N$), in a voltage-clamped muscle fibre are characterized by a sudden increase of the membrane current to a peak, followed by an exponential decay with a time constant τ of about 1 ms at room temperature (see control curves in figure 10). This decay time constant, and its dependence on membrane voltage and temperature, were in excellent agreement with the time constants derived from noise analysis (Anderson and Stevens, 1973). Therefore it was concluded that the decay of m.e.p.c. or e.p.c.$_N$ reflects the closing of open ion channels, according to the reaction

$$AR^* \xrightarrow{\alpha} AR$$

with τ approximately $1/\alpha$, rather than the decay of transmitter concentration in the synaptic cleft via hydrolysis and diffusion. This important conclusion, and other work, imply that a postsynaptic response like an m.e.p.c. is generated by a brief increase of ACh concentration in the synaptic cleft, which activates about 2000 ion channels within 300 µs. At the same time the free ACh concentration in the synaptic cleft declines rapidly to very low values, for the most part by binding of the ACh molecules to the ACh-receptors, the other part by binding to the ACh-esterase molecules (consider the close vicinity of presynaptic active zones and subsynaptic ACh-receptors in figure 2). When the open channels close, the bound ACh molecules dissociate from the recognition sites and become destroyed immediately by the ACh-esterase. Thus, the ACh concentration in the synaptic cleft is negligible during the decay phase of m.e.p.c. or e.p.c.$_N$, which therefore can be treated was a concentration jump experiment.

Properties of the acetylcholine receptors of the postsynaptic membrane

The receptor properties, mostly discovered during the past 10 years, can be summarized as follows.

(1) The ACh-R is an integral membrane protein which extends through the full thickness of the membrane (fig. 3).

(2) They are mainly localized at the crests of the junctional folds (fig. 2) at a density of 6000–7500 μm^{-2} in good agreement with about 9000 ion channels which can be opened at high concentrations of acetylcholine per µm length of terminal. One µm length of terminal covers 1–2 μm^2 of receptive area.

(3) Two to four α-BuTx binding sites are located on one ACh-R (fig. 3).

(4) At least two agonist molecules are required to activate one ACh-R in a co-operative manner.

(5) The time which the agonist–receptor complex needs to open the shut channel fully is $\leqslant 10\,\mu s$.

(6) The active state is associated with an open ion channel through which an elementary current of about 2 pA flows at the resting membrane potential. This elementary current produces a membrane depolarization of about 0.2 µV.

(7) The mean lifetime of an open channel is about 1 ms at room temperature and −80mV membrane potential. It depends on membrane potential with shorter closing times at depolarized values (e-fold change for about 100 mV) and on temperature with a $Q_{10} \simeq 2.7$. At 37 °C the ion channel is open for about 0.3 ms only. The time during which a channel stays open depends strongly on the agonist used, and varies over a 17-fold range, while the single channel conductance is almost constant for most of the agonist's (table I).

(8) The single channel conductance is in the range 20–25 PS with no, or at most slight, temperature dependence. However, in the mouse end-plate a sudden increase of the conductance was observed at temperatures greater than 25 °C with a new value of 45 PS in the range 34–39 °C. This could be the result of a phase transition in the lipid membrane and may indicate that the properties of the receptor and its channel are not only determined by the structure of the integral protein itself, but also by its environment.

TABLE I. *Properties of agonist-activated channels in normal motor end-plates at room temperature and about −80 mV membrane potential. *Values obtained using Tris-buffer which is known to reduce the conductance γ. For a comprehensive compilation of published data see Colquhoun (1979) and Wray (1980)*

Agonist	Single channel conductance (PS)	Mean lifetime of open channels (ms)
Acetylcholine	19–25	1
Carbachol	19–24	0.33
Suxamethonium	20*	0.23
Decamethonium	15*	0.16–0.45
Suberyldicholine	22–28	1.7–2.1
Nicotine	18*	0.22

(9) During the mean lifetime of 1 ms about 10^4 ions, mainly Na^+ and K^+, flow through the open channel. This large number is a strong argument for an open ion channel and excludes the possibility of an active carrier system.

(10) The net channel current reverses its direction near zero membrane potential, which is called the reversal potential of the channel. This value indicates an almost equal permeability of Na^+ and K^+ ions. The channel is impermeable to Cl^-. Many other mono- and divalent metal ions and organic cations can also penetrate the channel. The sequence of monovalent cations is $Th^+ > Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$ with permeability ratios relative to Na^+ of 2.5, 1.4, 1.3, 1.1, 1.0 and 0.9 (Adams, Dwyer and Hille, 1980). The most permeant organic cations include ammonium, hydroxylamine, hydrazine and guanidine with permeability ratios relative to Na^+ in the range 1.3–2.0. To a lesser extent also, larger molecules like trometamol (TRIS) and choline are permeant. From such experiments, it was concluded that, in its narrowest part, the open ion channel behaves like a square pore of 0.65 × 0.65 nm dimension with cut-off at each corner (Dwyer, Adams and Hille, 1980). On geometric grounds such a pore could also be permeable to many larger molecules such as acetylcholine, carbachol, suxamethonium and decamethonium. In conclusion the ACh channel seems to be rather non-selective compared with the Na^+ or K^+ channels involved in the action potential of excitable membranes.

(11) Considerable differences are found for the apparent dissociation constant *K*. The values are

28 μmol litre^{-1} for acetylcholine, 340 μmol litre^{-1} for carbachol and 18 μmol litre^{-1} for suberyldicholine (Dreyer, Peper and Sterz, 1978). For several reasons it is assumed that the efficacy of the natural transmitter ACh is rather large (about 90%). Another strong agonist, carbachol, has an efficacy of about 78% of that of ACh. Both affinity and efficacy contribute to the differences of potencies between agonists.

(12) The ACh-receptor properties are similar in the end-plates of different vertebrate species, including humans. An interesting finding derived from the analysis of membrane current fluctuations was that the ACh-receptors of human myasthenic muscles have unchanged channel properties compared with normal muscles. The reduced end-plate response in the myasthenic disorder is the result of a reduced number of ACh-receptors which can be activated by the release of transmitter quanta (Cull-Candy, Miledi and Trautmann, 1979).

(13) In normal nerve–muscle preparations ACh-R have a low density outside the subsynaptic membrane. The density of these extrajunctional ACh-R is high in developing and denervated muscles. Their properties differ in some respects from those of junctional receptors. Their turnover rate is much faster than of those in the junctional region. While the reversal potential and therefore the cation permeability of the open extrajunctional channel is unchanged, the channels stay open for a longer time by a factor of three and the elementary current may be somewhat reduced compared with junctional channels.

(14) Recent experiments on frog muscles demonstrated that transmitter-activated ion channels on the postsynaptic membrane of fast and slow muscle fibres differ in their lifetimes and conductances (Miledi and Uchitel, 1981). The ion channel properties at the slow muscle end-plates are similar to those of the ion channels associated with extrajunctional ACh-receptors in fast muscle. The differences raise a number of questions about the factors which determine the ACh-receptor properties. It is known that muscle fibres are under neural control and it may be that the receptor properties are determined by the type of nerve which innervates the muscle.

COMPETITIVE ANTAGONISM

Tubocurarine is one of the classical examples of a competitive antagonist (Jenkinson, 1960). This mechanism is included in the sequential reaction scheme shown in figure 8. The classical method used to study antagonist action is to measure the shift of the dose–response curves produced by various antagonist concentrations. In the case of a pure competitive inhibition it is predicted that the dose-ratio will be given by the Schild-equation: $r = 1 + C_I/K_I$, for a wide range of theories of agonist action including co-operative models (Colquhoun, 1973). The dose ratio r is the factor by which the agonist concentration must be increased to maintain a constant response in the presence of an antagonist concentration C_I. K_I is the equilibrium dissociation constant. Because it is difficult to measure concentration–conductance curves at high agonist concentrations, dose ratios have been measured in most studies under conditions in which only a small fraction of receptors was occupied by the agonist, so the test was not very critical for competitive inhibition.

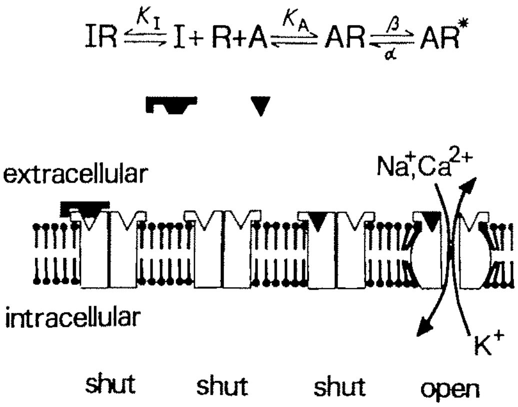
$IR \underset{}{\overset{K_I}{\rightleftharpoons}} I + R + A \overset{K_A}{\rightleftharpoons} AR \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} AR^*$
extracellular
Na^+, Ca^{2+}
intracellular
K^+
shut
shut
shut
open

FIG. 8. Reaction scheme of the action of competitive antagonists like tubocurarine, with ACh-receptors. This scheme ignores the well known co-operativity (see fig. 3). I = competitive inhibitor; K_I = equilibrium dissociation constant for the binding of the antagonists to the recognition sites.

ION CHANNEL-BLOCKAGE, A NEW FORM OF DRUG–RECEPTOR INTERACTION

A number of drugs are known to modify the agonist-induced membrane depolarization in a non-competitive manner. The mechanism of this behaviour remained obscure, or was attributed to an acceleration of desensitization by these drugs. Some drugs such as local anaesthetics not only reduced the amplitude of end-plate currents, but also produced a characteristic biphasic time-course of their decay phase, an early brief

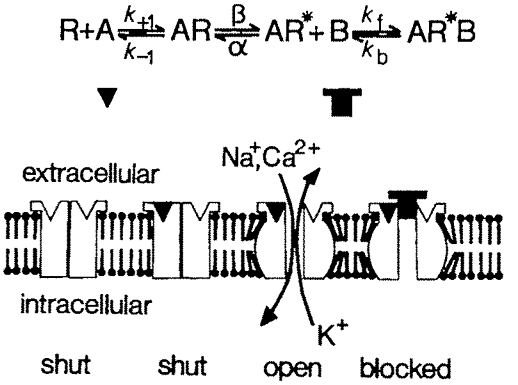

FIG. 9. Reaction scheme of the channel-blocking mechanism. This scheme ignores the well known co-operativity (see fig. 3) and the possibility that the blocking drug may bind to the ion channel in its shut conformation. B = blocking drug; AR* = activated agonist–receptor complex associated with an open ion channel; AR*B = a state associated with a blocked open ion channel. k_f and k_b = forward and backward rate constants for the blocking and unblocking reaction.

component followed by a greatly prolonged one. This could not be explained in the classical theory of competitive inhibition. The original hypothesis that the ACh-R has separate Na^+ and K^+ channels and that the action of local anaesthetic molecules is the result of different influences on these channels could not be verified. In recent years evidence accumulated that the local anaesthetics (Steinbach, 1968a,b) and many other drugs may interact with the ACh-R at a site distinct from the agonist recognition site. Adams (1976) then explained the action of barbiturates on end-plate function by a direct binding to and blocking of open ion channels, a mechanism first proposed by Blackman (1959) for the action of hexamethonium on ganglion cells. This is a very attractive model because it offers a clear physical picture of the blocking action, as shown in figure 9. The drug molecules try to pass the open ion channel, thereby plugging the channel like a cork in the neck of bottle.

The simplest reaction scheme which so far explains the block of open end-plate channels by drugs is an extended reaction scheme of equation (1) (see also fig. 9):

$$A+R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} AR \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} AR^{\star}+B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} AR^{\star}B \qquad (3)$$

The blocking molecule B binds solely to the activated state AR* leading to the state AR* B, the conductance of which is assumed to be zero. k_f and k_b are the forward and backward rate-constants of the channel-blocking process. At least for the local anaesthetics, it has been confirmed by single channel experiments that the blocked state AR* B has a zero channel conductance (Neher and Steinbach, 1978). Further the data could only be explained with the assumption that the state AR* B changed back only to the open state AR*. Therefore it seems to be justified to describe the channel-blocking process by a sequential reaction scheme, at least at moderate concentrations of blocker, but it is still a very simple one because it does not take into account the well known co-operativity of the agonist–receptor interaction (fig. 3) and the possibility that blocking drugs may also bind to ion channels being in a closed conformation.

How can channel-blocking be observed?

A blocking drug shows the behaviour of a non-competitive inhibitor. While at low agonist doses the response is only slightly reduced, this effect becomes more pronounced with greater agonist or blocker concentrations, or both, so the maximum response is depressed, and the dose–response curve is shifted to the right.

Most information about the blocking reaction can again be obtained from concentration- or voltage-jump relaxation methods, from observations of single ion channels and from the analysis of agonist-induced membrane current fluctuations. Assuming a fast binding of agonist to the receptor, the ion channel can exist in three kinetically distinguishable states in the presence of a blocking drug. Thus the blocking mechanism predicts the occurrence of two exponential components in relaxation experiments as well as in experiments at equilibrium. With low agonist concentration such that only a small number of receptors are activated, the following relationship is predicted:

$$\tau_f^{-1}+\tau_s^{-1}-\tau^{-1} = k_f \cdot C_B + k_b \qquad (4)$$

with τ_f and τ_s the time constants for the faster and slower components, respectively, and τ the time constant in the absence of the blocking drug. The conditions are always $\tau_f < \tau < \tau_s$. Such relaxation experiments at different drug concentrations C_B allow the estimation of the two rate constants k_f and k_b in the blocking reaction according to equation (4).

In figure 7A the relaxation of an agonist-induced end-plate current after a membrane voltage jump is demonstrated. In the presence of a blocking drug, quite different time-courses can be observed depending on the rate constants of the blocking process. An example is given in figure 7B for tubocurarine, which dissociates from the blocked channels relatively slowly (Colquhoun, Dreyer and Sheridan, 1979). While the time-course of the current in the beginning is only slightly faster, the peak current is not maintained. The end-plate current decreases slowly in an exponential manner to a smaller value (inverse relaxation) reflecting a slow voltage-dependent blockage of open channels. If the slow component is much slower than the fast one and if the antagonist concentration is small, then the slow time constant is approximately:

$$\tau_s^{-1} \simeq k_b \qquad (5)$$

It should be mentioned that fast blockers like procaine or gallamine have the fast component, τ_f, in the inverse direction.

Drug-induced alterations of the time courses of m.e.p.c. or e.p.c.$_N$ are good indications that drugs may act with a site of the ACh-R distinct from the recognition site. Depending on the rate constants for blocking and unblocking the decay phase of an m.e.p.c. or e.p.c.$_N$ can be changed in the presence of a blocking drug (fig. 10): (1) the end-plate current decays as the sum of two exponential components with fast and slow time constants (fig. 10B) as predicted by equation (4); (2) the current decay can still be fitted by one exponential function, but with a reduced time-constant compared with the control (fig. 10C). This happens when the dissociation from the blocked channels is very slow. Then the number of channels which change from the blocked to the open state will always be small per unit time and therefore the corresponding slowly-decaying current is often not measurable.

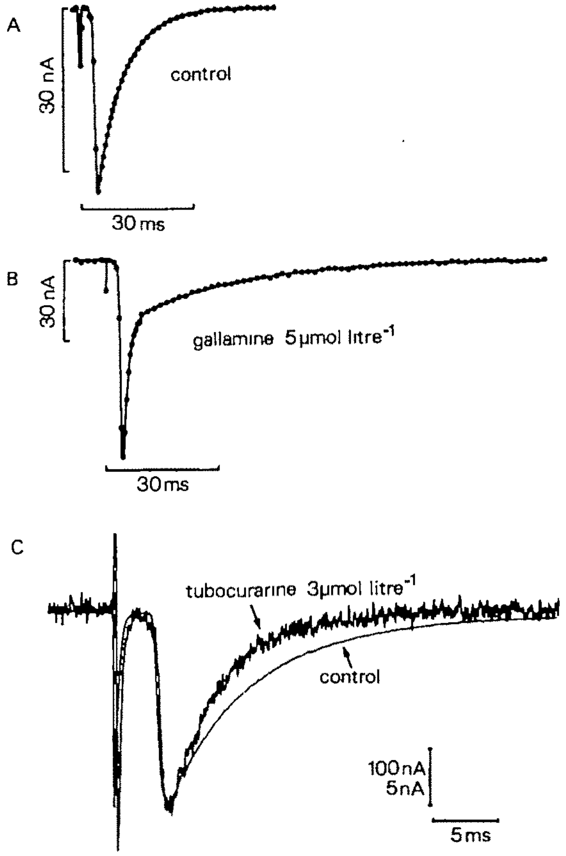

FIG. 10. Alterations in the amplitude and decay phase of nerve-evoked end-plate currents as a result of the presence of blocking drugs like gallamine (B) and tubocurarine (C). The end-plate currents are downwards according to their inward direction. A: Average of seven control end-plate currents in calcium 0.5 mmol litre^{-1}. Decay phase is fitted with one exponential with time constant $\tau = 7.1$ ms. B: One end-plate current in gallamine 5 μmol litre^{-1} and calcium 0.75 mmol litre^{-1}. The decay phase becomes biphasic and can be fitted with the sum of a fast and slow exponential component of the time constants $\tau_f = 1.37$ ms and $\tau_s = 28.1$ ms, respectively. Digitized records, membrane potential −130 mV, temperature 12.4 °C (reproduced from Colquhoun and Sheridan, 1981, with permission). C: End-plate currents in the absence and presence of tubocurarine. The currents with and without tubocurarine are scaled to the same height. The control has an amplitude of 332 nA and a decay time constant of 6.1 ms. In the presence of tubocurarine 3 μmol litre^{-1} the amplitude is reduced to 17.7 nA (so the record looks noisier), and the time constant for decay is reduced to 3.6 ms because of the blockage of open channels. Membrane potential −140 mV, temperature 11 °C (reproduced from Colquhoun, Dreyer and Sheridan, 1979, with permission).

The blocking process and especially its possible consequence during tetanic nerve stimulation can be nicely demonstrated in an ionophoretic double-pulse experiment if the dissociation of the drug molecules from the channel is slow compared with the duration of the agonist responses (Adams, 1976; Katz and Miledi, 1978; Dreyer et al., 1979). In figure 11 the first ionophoretically-applied agonist pulse (conditioning pulse) opens ion channels and allows the drug molecules to block a fraction of them. Therefore a second ionophoretic agonist pulse (test pulse)

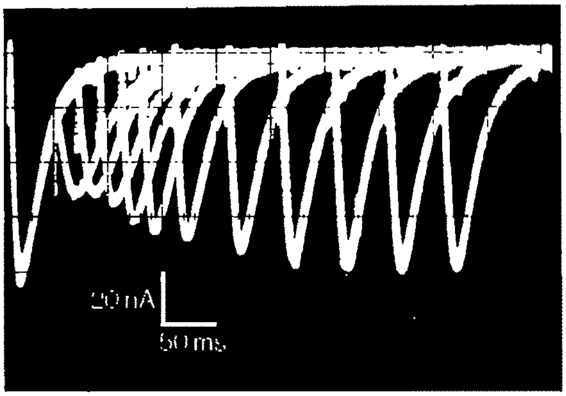

FIG. 11. Double-pulse experiment demonstrating the blocking and unblocking process of ACh-activated ion channels as a result of the presence of prednisolone 100 µmol litre^{-1}. Conditioning and test-pulses were elicited by the same amount of ACh applicated ionophoretically through a micropipette directly at the end-plate. For further explanation see text. The time constant for the unblocking reaction is about 80 ms. Voltage-clamped end-plate of a frog cutaneus pectoris muscle fibre at −85 mV membrane potential (Dreyer, Peper and Sterz, unpublished data).

should elicit a reduced response if it follows closely on the first one, since now fewer ion channels are available for activation. With larger time delays between both pulses more and more channels have time to unblock. Therefore the test pulse is less and less depressed until the amplitudes of the first and second pulses are the same. The depression of the test pulse amplitudes in relation to the time between conditioning and test pulses gives an exponential time-course with a time constant corresponding in the first approximation to the slow unblocking time k_b^{-1} (equation (5)).

Single ion channel recording. Recording single channel currents, Neher and Steinbach (1978) could directly demonstrate the alteration of a single open channel by local anaesthetics. The result of such an experiment is illustrated in figure 12. In the absence of a blocking drug the agonist-activated channel opens and a constant current flows for a random time (fig. 12A). In the presence of a blocking drug like the local anaesthetic benzocaine, the ion channel opens, but then switches rapidly between the open and blocked state, producing a burst of short pulses (fig. 12B, C). The burst length is longer than the normal open time which explains the occurrence of the slow component for example in relaxation experiments (figs 7 and 10). The sum of all short open periods is on average equal to the mean open time of the unmodified channel. Further, the burst duration increases with increasing drug concentrations. Both facts indicate that an open, but blocked channel AR^*B cannot change directly into the shut state AR, confirming the sequential reaction scheme of blocking mechanism. The single channel recording also showed clearly that during the blocked state AR^*B the channel current is zero (fig. 12C).

Properties of channel-blocking drugs

For a number of drugs evidence exists that their action on the neuromuscular transmission is a result of the blocking of open ion channels. Not all drugs have been studied quantitatively to obtain kinetic parameters. The drugs may be classified as follows:

(1) Drugs that can block open ion channels, for example barbiturates, local anaesthetics, atropine, prednisolone, amantadine, quinacrine, ethidium bromide and some antibiotics. However, many of these have other, usually poorly understood, actions especially at higher concentrations. Most of these drugs probably have a higher affinity to the channels in their opened than in their closed conformation. Part of the problem is that many studies have not looked at equilibrium responses, but only kinetics. At equilibrium the inhibition of the response seems often to be greater than expected from open channel block.

(2) The classical competitive antagonists such as tubocurarine and gallamine, which have a high affinity to the recognition sites as well as to the ion channels in their open conformation.

(3) Drugs such as decamethonium which can open the ion channel, and then block it once it has opened. This self-blocking action could give the appearance of partial agonism, but it is not yet known to what extent such effects are responsible for the low maximum response that some agonists produce.

The forward (association) rate constant k_f is similar for all these drugs with a value in the range of 10^7 mol^{-1} s^{-1}. For cationic drug molecules this value depends on membrane potential in an exponential manner with greater values at hyperpolarized levels because the probability of sticking in the channel is increased. The similar association rate constants suggest that the molecular structure of the blocking drugs does not importantly influence the binding to the open ion

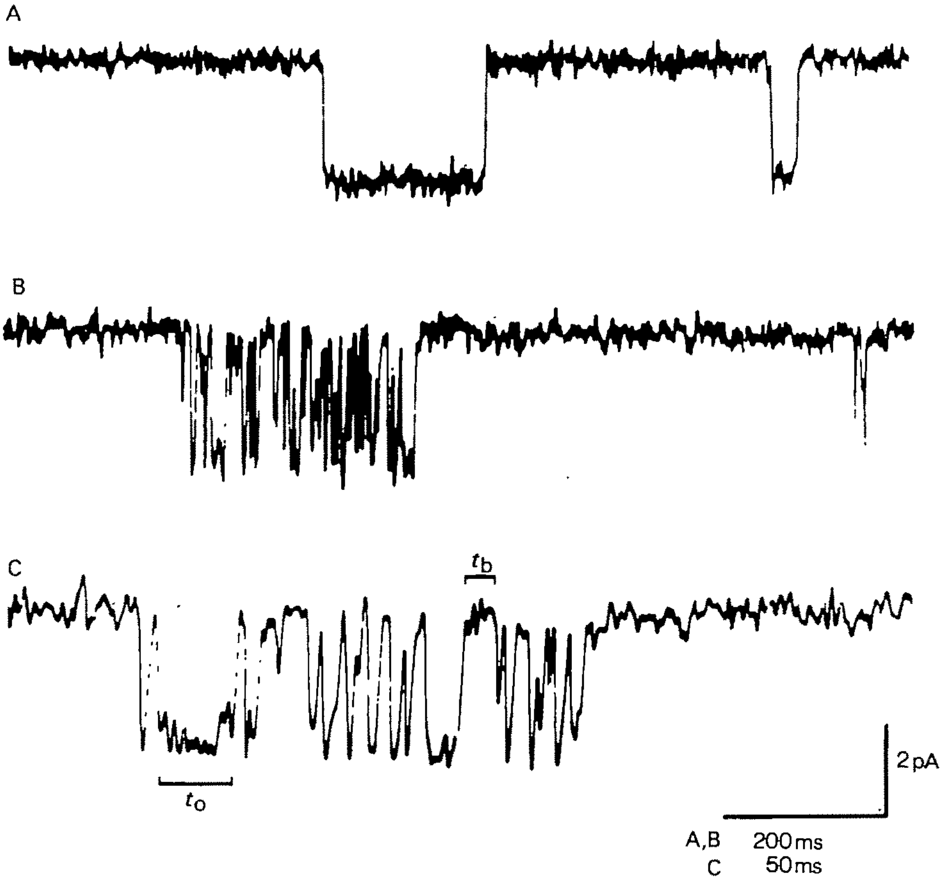

FIG. 12. Effects of the local anaesthetic benzocaine on single, acetylcholine-activated channel currents, recorded with the patch-clamp method. The currents activated in the presence of acetylcholine 100 nmol litre^{-1} are shown as a downward deflection indicating an inward current. A: Single channel currents in the absence of benzocaine (see also fig. 6). Membrane potential −110 mV, temperature 9 °C. B: Single channel currents in the presence of benzocaine 200 µmol litre^{-1}. Records were obtained from the same muscle as in A, but with a different fibre. Membrane potential −130 mV, temperature 9 °C. C: A burst in benzocaine 200 µmol litre^{-1} (from the same run as B at better time resolution). The brackets indicate one open interval, t_o, and one blocked interval, t_b. The mean number of blockages, the mean lifetime of the open and the blocked intervals and the mean length of such bursts are determined by the forward and backward rate constants and the concentration of the blocking drug. Recordings obtained from the extrajunctional membrane of 4–6 week denervated semitendinosus muscle fibres of the frog (reproduced from Ogden, Siegelbaum and Colquhoun, 1981, with permission).

channel, which is probably mainly governed by diffusion of the molecules to a site located inside the channel. In contrast, major variations are found in the unblocking (dissociation) rate constant k_b. The mean blockage time $1/k_b$ is in the range of milliseconds for procaine and gallamine and of seconds for tubocurarine. For charged molecules, the recovery from blockage depends on membrane potential and can be speeded up with depolarization. Both rate constants allow the calculation of the channel-block equilibrium constant $K_B = k_B/k_f$. For references to channel-blocking agents see Colquhoun, Dreyer and Sheridan (1979) and Adams (1981). A comprehensive compilation will be given by Peper, Bradley and Dreyer (1982).

Channel-blocking drugs do not change the endplate reversal potential, and therefore do not change the relative permeability of the ion channel for Na$^+$ and K$^+$ ions. Thus the ACh channel could be pictured as a pore with a large outer mouth, but it is difficult to estimate the

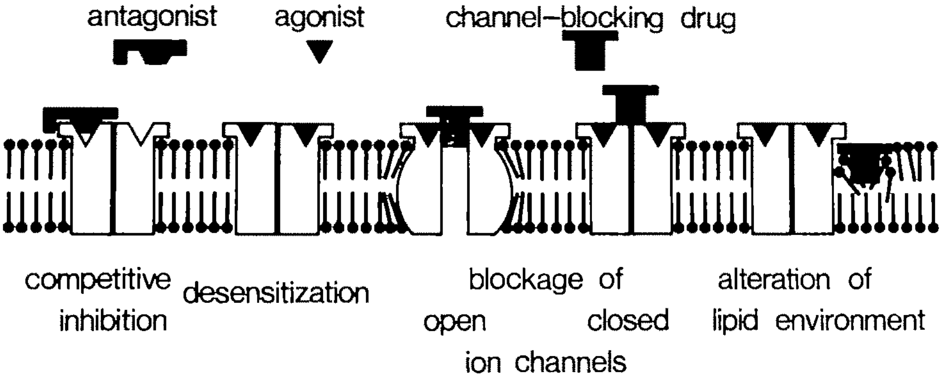

FIG. 13. Possible modes of action of drug molecules on acetylcholine receptors hindering the flow of ions through channels.

dimension of the channel mouth on the basis of the chemical structure of the blocking drugs.

So far it has been assumed that drug molecules can only act with the recognition site or with a site in the open ion channel, or both, but it should be kept in mind that, from the experiments, no distinction can be made between plugging an open ion channel and binding to an active agonist–receptor complex, thereby allosterically shutting the ion channel. In addition other mechanisms are known, or may be possible, which prevent the ion channel opening. Some of these are illustrated in figure 13 and may be summarized as follows:

(1) Binding of a competitive inhibitor to the recognition site preventing ACh-receptor activation.

(2) Desensitization produced by long exposure of agonist to the ACh-receptor. Some channels enter a long-lived shut state which cannot be opened by ACh (Sakmann, Patlak and Neher, 1980); they recover slowly to the resting state on removal of the agonist molecules. Some drugs may promote desensitization.

(3) Drug-induced blockage of open ion channels preventing not only the closing of the channels, but the flow of ions also.

(4) Binding of drug molecules to the ion channel in its shut conformation preventing the opening of the channels.

(5) Alteration of the lipid environment of the ACh-receptors, thereby changing the channel properties (probably the action of alcohols).

The importance of channel-blocking for neuromuscular transmission

Channel blockage should always be taken into account as a possible way in which drugs of quite different chemical structure could influence neuromuscular transmission. An important characteristic of channel block by many drugs is that the channels must first be opened to become blocked, so the effect is intensified by all actions which open more channels, as do depolarizing muscle relaxants, cholinesterase inhibitors and high frequency nerve stimulation. Therefore it can be termed a use-dependent effect. Further, the blockage is more effective when the blocking drug concentration is high as expected from the reaction scheme of the blocking mechanism. Normally, channel blockage produces only a relatively small effect on the peak amplitude of end-plate responses. Therefore neuromuscular transmission, with its high safety factor, is unaffected unless this factor is reduced. Then a small contribution of channel block may be sufficient to reduce the end-plate response below the threshold for a muscle action potential. This could well explain the effect of many drugs such as some antibiotics, anticonvulsants etc., which deepen the myasthenic reaction.

A drug-induced channel block cannot be antagonized by a cholinesterase-inhibitor. On the contrary, the prolonged action of ACh in the synaptic cleft will increase the probability of channel block (Dreyer, unpublished observations). This may be the reason why, sometimes, cholinesterase inhibitors cannot abolish a neuromuscular block in the presence of putative channel blockers such as some antibiotics.

One may ask what is the importance of the channel blocking property of tubocurarine compared with its competitive action? Although tubocurarine has a high affinity (0.12 μmol litre^{-1}) for the open ion channel, the main effect on the ACh-R is still the competitive action on the agonist recognition site with an affinity of about 0.34 μmol litre^{-1}. The reason for this is that, during an m.e.p.c. or e.p.c.$_N$, only relatively few channels are open. On the other hand, it has been reported that in curarized nerve–muscle preparations the muscle contractions and the amplitudes of end-plate potentials decrease progressively during short tetanic nerve stimulation. This has been taken as strong evidence for a presynaptic action of curare thereby interfering with the transmitter release process (Miyamoto, 1978; Glavinovic, 1979). The explanation may probably be simpler. During tetanic stimulation the use-dependent channel-block of tubocurarine contributes appreciably to the neuromuscular block, thereby deepening the paralysis. The time between the stimuli may be too short to allow the unblocking of the blocked ion channels caused by the foregoing end-plate potentials. This reduces the number of ACh-R which can be activated, and so the e.p.p. amplitudes during tetanic nerve stimulation. Such use-dependent blocks are well known from the action of local anaesthetics on Na$^+$ channels of nerve fibres. Also, the differences in the twitch tension depression and in the time-course of tetanic fade, comparing drugs such as hexamethonium, pancuronium and tubocurarine, could probably be explained by different affinities of these drugs for the recognition sites and the open ion channels of postjunctional ACh-receptors without assuming a prejunctional action (Bowman, 1980). Tetanic fade is not restricted to acetylcholine-like antagonists. On the contrary, it is typical for channel-blockers and can also be caused by neutral molecules. To discuss this in detail is beyond the scope of this article and will be undertaken elsewhere.

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RELEASE OF TRANSMITTER AT THE NEUROMUSCULAR JUNCTION

F. G. STANDAERT

Neuromuscular transmission has been investigated vigorously for more than a century and more is known about it than about any other synaptic function. Yet, our understanding is still incomplete. Available information describes the skeleton of the system, but gives only glimpses of the dynamic processes that make it lively. The basic theory is plausible and supported by a large body of data, yet it is neither fully explanatory, nor beyond challenge.

The theory holds that transmitter is stored in and is released from motor nerve endings as uniformly sized packages, or quanta. This idea began with the observation of small, spontaneous, depolarizing potentials at neuromuscular junctions (Fatt and Katz, 1950). These potentials are only about 1/100 the amplitude of the end-plate potential (e.p.p.) evoked when the motor nerve is stimulated, but except for size, they resemble the e.p.p. in their time-course and in the ways in which they are affected by drugs (Fatt and Katz, 1952). Therefore, they were called miniature end-plate potentials (m.e.p.p.). Statistical analysis led to the conclusion that m.e.p.p. are unitary responses; that is, there is a minimum size for the m.e.p.p. and all are either this size or a multiple of it (del Castillo and Katz, 1954). Since m.e.p.p. are too big to be produced by a single molecule of acetylcholine, it was deduced that they are produced by uniformly-sized packages, or quanta, of transmitter. It was further shown that the amplitudes of end-plate potentials evoked by nerve stimulation vary in discrete units, each the size of an m.e.p.p., and from this it was deduced that the e.p.p. is produced by many quanta released simultaneously (Boyd and Martin, 1956).

At about the same time that m.e.p.p. were discovered, electron microscopy of neuromuscular junctions showed the nerve endings to be rich in small, round, electron-transparent structures (Palade, 1954; Palay, 1954; Robertson, 1956). Because these structures, or vesicles, were uniform in size and were congregated near the synaptic surface of the nerve ending, it was logical to postulate that they were anatomical correlates of m.e.p.p., that is each vesicle held one quantum of transmitter (del Castillo and Katz, 1955). Thus, it came to be believed that the release of transmitter from motor nerves is quantized; the m.e.p.p. is produced by the release of the quantum of transmitter contained in a vesicle, and the stimulus-evoked end-plate potential (e.p.p.) is the depolarization produced by the synchronous discharge of several hundred vesicles (Martin, 1966).

Almost all modern research is based on this hypothesis. The postulate that an m.e.p.p. is caused by a quantum of transmitter and that an e.p.p. is the response to a number of quanta allowed electrophysiologists to develop statistical methods for analysing neuromuscular transmission and the idea that each quantum is contained in a vesicle gave morphologists a way to observe transmitter in motor nerve endings. As a result, the vision of neuromuscular transmission that emerges from physiological studies is almost universally described with reference to the vesicles seen via the electron microscope.

Modern electron microscopy of the neuromuscular junction provides remarkable pictures of nerve endings and the vesicles in them. Figure 1 is a transmission electron micrograph of a longitudinal section through a frog motor nerve ending. It is apparent that the contents of the ending are not homogeneous. The vesicles are congregated in the portion toward the junctional surface, and microtubules, mitochondria and other support structures are aligned toward the opposite side. More pertinent is the arrangement of the vesicles. They are ordered in a repeating pattern of triangular arrays with the apex of each

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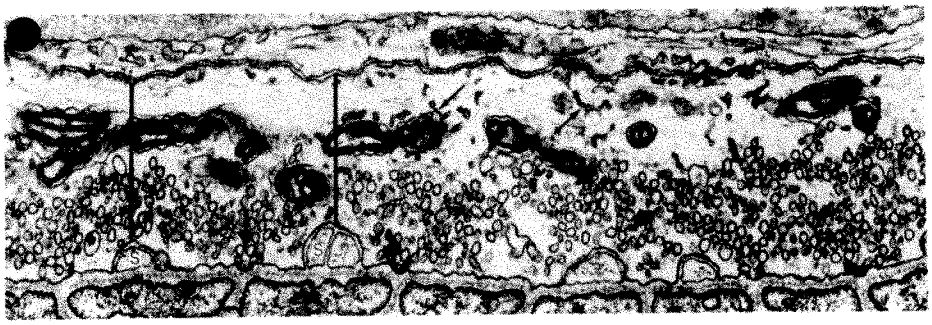

FIG. 1. Longitudinal section of frog neuromuscular junction. The nerve ending is in the centre, between the Schwann cell sheath (top) and the postjunctional membrane (bottom). Vesicles are concentrated on the junctional side, mitochondria and microtubules on the other side. Prejunctional densities, or active zones (large arrow), are opposite postjunctional clefts. Schwann cell processes (s) insinuate periodically between nerve and muscle. (From Heuser and Reese (1973). Reproduced with the permission of *J. Cell Biol.*)

triangle enclosing a small, electron dense, thickened patch of membrane. This thickened area is a cross-section of a transverse band that runs across the width of the synaptic surface of the nerve ending. These bands are seen more clearly in pictures of the surface of the nerve ending made by scanning electron microscopes (fig. 2). Because the bands seem to be part of a system that orients the vesicles in the nerve ending and controls their sites of release, they are referred to as "active zones". The active zone is about 50 nm wide and has about 50 vesicles close to it and many more vesicles in the array above it. There are between 500 and 1000 active zones in a nerve ending (Peper et al., 1974; Ceccarelli and Hurlbut, 1980a).

Although it is very difficult to catch vesicles in the act of discharging their contents, a strong argument has been made that the depressed areas, or pits, alongside the bands in figure 2 are the residue of vesicles that erupted through the nerve membrane and discharged their contents into the junctional cleft (Heuser et al., 1979; Ceccarelli and Hurlbut, 1980a; Heuser and Reese, 1981). It is significant that the number of pits increases with time after stimulation (fig. 3) and that they are almost always in rows along the sides of the bands. Because each active zone is aligned exactly with a secondary cleft in the end-plate (fig. 1), the sides of the band are precisely over the shoulders of the junctional folds that form the secondary cleft, where nicotinic cholinoceptors are found in greatest density (Land, Salpeter and Salpeter, 1980). Thus the system appears to be constructed

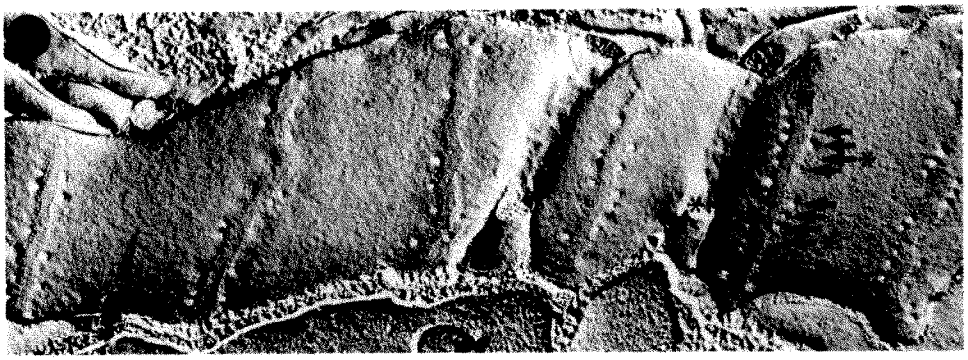

FIG. 2. Freeze-fractured section of frog nerve ending. Active zones appear as bands transversing the nerve ending. Pits (plain arrows) alongside the bands may be the residue of discharged vesicles. Particles (asterisked arrows) may be specialized proteins associated with vesicles. (From Heuser and colleagues (1979). Reproduced with the permission of *J. Cell Biol.*)

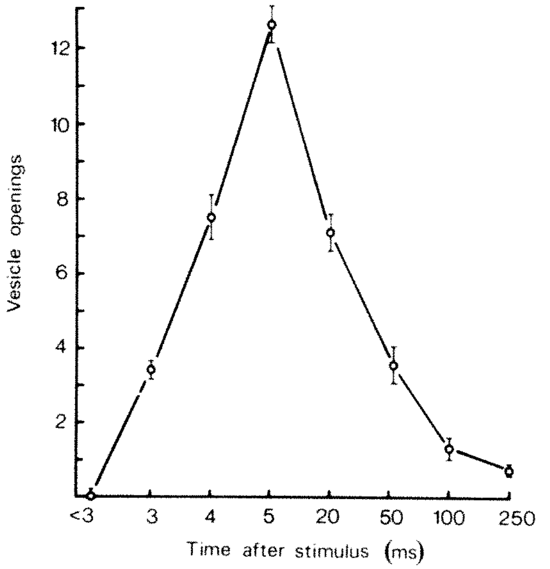

FIG. 3. Number of pits along an active zone as a function of time after stimulation. Frog neuromuscular junction treated with 4-aminopyridine. (From Heuser and Reese (1981). Reproduced with the permission of *J. Cell Biol.*)

so that vesicles extrude transmitter precisely onto receptors. Moreover, the depths of the secondary clefts and the crowns of the junctional folds contain cholinesterase (Salpeter, 1967), exactly where it should be if it were to destroy acetylcholine that diffuses away from the receptors. It is hard to imagine how a system for chemical transmission could be laid out more efficiently.

Figures 1, 2 and 3 are from frogs, but the neuromuscular junctions of mammalians are similar. Mammalian nerve endings are globular, not linear as in the frog, and because of this the active zones are shorter and there are fewer vesicles associated with each (Ellisman et al., 1976), but otherwise both types have the same elements in the same arrangement.

An action potential is the normal activator for this system but, *per se*, it does not trigger the release of transmitter. That function belongs to a calcium flux initiated by the action potential (Katz and Miledi, 1965, 1967, 1969a, b). Neither sodium flux nor depolarization will produce the release of transmitter if calcium is not present and the addition of calcium to a nerve ending, as by microinjection or via exogenous calcium ionophores inserted into the membrane, will release transmitter even if the nerve is not depolarized (Miledi, 1973; Ito and Miledi, 1977). Moreover, the number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionized calcium in the extracellular fluid. Several investigators have produced data showing that the change in quantal content of an e.p.p. is proportional to the fourth power of the change in calcium concentration, that is doubling the calcium results in a 16-fold increase in quanta (Dodge and Rahamimoff, 1967). One interpretation is that calcium ions co-operate strongly with each other in the release process (Bennett and Lavidis, 1979; Andreu and Barrett, 1980; Dunant, Babel-Guerin and Droz, 1980).

It is not only the concentration of calcium that influences the amount of transmitter released, but also the length of time during which the calcium flows into the nerve ending, that is the quantal content of the e.p.p. is a function of the total number of calcium ions in the ending after a nerve is stimulated. The calcium current begins about the time the action potential approaches its maximum depolarization and persists until the membrane is returned to its normal potential by outward fluxes of potassium. Because potassium efflux normally ends the calcium current, the flow of calcium can be prolonged by drugs, such as 4-aminopyridine, which slow or prevent the potassium current (Thesleff, 1980). The increase in quantal content produced in this way can reach astounding proportions. In a recent study Katz and Miledi (1979) determined that an e.p.p. in frog muscle normally contains about 400 quanta, but those evoked in the presence of the potassium antagonists 3,4-diaminopyridine or tetraethylammonium might contain as many as 80 000 quanta. The latter is twice the number of vesicles aligned along active zones of a frog nerve ending and ready for release, but the period of transmitter discharge is prolonged so greatly by these drugs (fig. 4) that there is time for additional vesicles to be mobilized from reserves and to be released.

Calcium is presumed to enter the nerve via special proteins that form channels through the nerve membrane. There is some thought that the calcium channels most intimately involved in the release of transmitter are located along the active zones (Ceccarelli et al., 1979; Ceccarelli and Hurlbut, 1980b; Pumplin, Reese and Llinas, 1981). These channels are opened by the action potential, either directly (Katz and Miledi, 1969a;

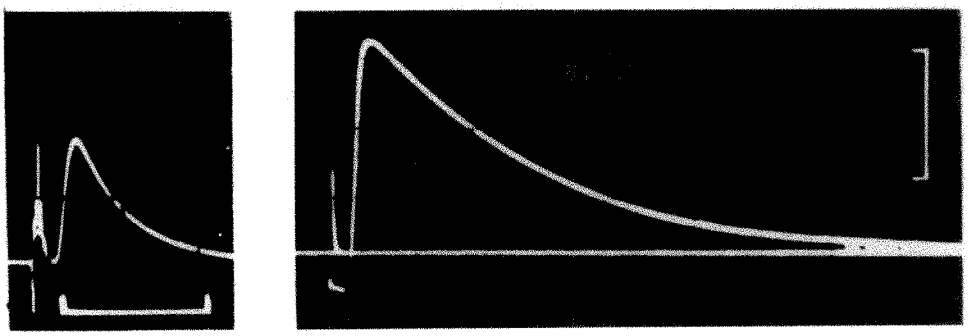

FIG. 4. Effects of 3,4-diaminopyridine on amplitude and time-course of end-plate current in frog neuromuscular junction. Left: control; right: in presence of diaminopyridine. Time scale 20 ms left; 90 ms right. Amplitude scale 0.3 μA left; 2 μA right. (From Katz and Miledi (1979). Reproduced with the permission of *Proc. R. Soc. Lond. B.*)

Llinas, Steinberg and Walton, 1976) or by cAMP formed during the action potential (Standaert and Dretchen, 1979, 1981). Calcium may also enter in an exchange with sodium via an antiporter—a system that carries sodium in one direction and calcium in the other. In the resting nerve the antiporter carries sodium into the cytoplasm and calcium out of it (Blaustein and Oborn, 1975), but at the peak of the action potential the system can reverse to carry sodium out and calcium in (Mullins, 1976).

The concentration of free calcium ions inside a nerve normally is about 10^{-7} mol litre^{-1} (Baker, 1978), about 1/10 000 of that outside the nerve. This says that there is a very strong gradient to drive the ion into the nerve, but the low internal concentration of free ion also says that there are very efficient processes for trapping calcium that does enter and for sequestering it until it is extruded. One consequence is that free calcium ions do not diffuse very far in the cytoplasm (Llinas and Heuser, 1977) and therefore they must either act very close to where they enter, or act indirectly by binding to a protein, most likely the one known as calmodulin, which initiates a sequence of reactions leading to discharge of transmitter (De Lorenzo, 1980).

The exact mechanism by which calcium causes release of transmitter is not yet known, but the presence of the ion in the area of the active zone seems to initiate a process in which the vesicle membrane fuses with the cell membrane and thereby connects the interior of the vesicle to the extracellular space of the junctional cleft. Transmitter leaves the opened vesicle and crosses the junctional cleft to react with cholinoceptors or be destroyed by cholinesterase, or both.

The fate of the empty vesicle is of considerable interest. It may be re-used; that is, after its contents are discharged the vesicle may reseal, retract into the cytoplasm and refill with transmitter, but current thinking favours the idea that vesicles collapse totally into the nerve membrane and disappear (Heuser et al., 1979; Zimmermann, 1979; Heuser and Reese, 1981). That is, once the vesicle membrane fuses with that of the nerve, the process goes to completion with the vesicle flattening out and adding its membrane to that of the external surface of the nerve ending. This postulate raises the question of what happens next. That something must happen becomes apparent from the information that the total amount of membrane in the vesicles (i.e. their total surface area) is far greater than the membrane in the surface of the nerve and that it is physically impossible continuously to add membrane from vesicles to nerve; at some point, membrane must be removed or the surface of the ending would grow to impossible dimensions (Bittner and Kennedy, 1970; Marchbanks, 1979). Furthermore, new membrane for new vesicles cannot be synthesized in the nerve ending; only the cell body has the capacity to make new membrane and it can neither make enough nor transport it quickly enough to keep up with the needs of an actively secreting nerve. There must be a system for removing material from the surface membrane and re-using it.

Photographic evidence in support of a system of membrane recycling has been provided by several investigators. Heuser and his associates examined neuromuscular junctions flashfrozen at carefully timed intervals after stimulation (Heuser et al., 1979; Heuser and Reese, 1981) and obtained electron micrographs that are compatible with the idea that vesicular membrane becomes mixed with the cytoplasmic membrane and is retracted from it to form new vesicles. For example, figure 5 contains a sequence that seems to show vesicles fusing and flattening out. It also shows large particles that Heuser and Reese believe to be a unique protein that can be used as a marker to locate vesicle membrane that entered the cell's surface. The number of these particles increases when the nerve is stimulated, suggesting that vesicles have collapsed into the surface membrane of stimulated nerves. Corollary evidence is found in electron micrographs of nerves treated with black widow spider venom (Ceccarelli et al., 1979; Hurlbut and Ceccarelli, 1979), a toxin that greatly increases the rate of transmitter release and may interfere with retraction of membrane. These photographs suggest that the venom produces a great increase in the surface area between active zones, as might be expected if vesicular membrane were added more rapidly than it could be removed.

With regard to the retrieval and re-use of vesicle membrane, Heuser and Reese (1973) and others (e.g. Gennaro, Nastuk and Rutherford, 1978) call attention to "coated vesicles" which appear after stimulation and they suggest that these are adolescent vesicles—spheres of membrane that have been extracted from the surface between active zones and are in the process of being turned into vesicles filled with transmitter. Although the nature of the coating is not known, it seems to be a protein (Pearse, 1976) and it has been suggested (Heuser and Reese, 1973) that it might be part of the mechanism that pulled membrane out of the nerve surface or that it might be part of a system for transporting acetylcholine into the vesicle.

Repeated stimulation requires the nerve ending to replenish its stores of releasable transmitter, a process known as mobilization. Strictly speaking, mobilization is a specific parameter derived from the statistical analysis of e.p.p. (Elmqvist and Quastel, 1965), but commonly the term is applied to the aggregate of all steps involved in maintaining the nerve ending's capacity to release transmitter; everything from the acquisition of choline and the synthesis of acetylcoenzyme A to the movement of vesicles to the release site. The dynamics of the individual steps are difficult to study and despite the obvious importance of

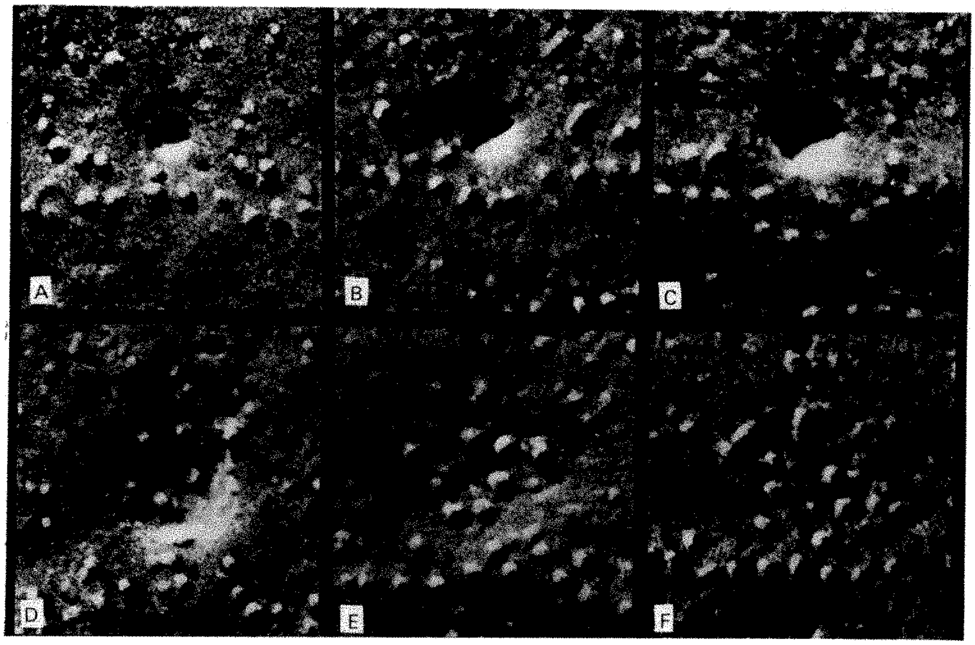

FIG. 5. Section of freeze-fractured frog nerve ending showing change in appearance of pits with time after stimulation. A = 3.7 ms; B, C and D = 5.2 ms; E = 20 ms; F = 50 ms. Note the large particles in the pit in D and the membrane in E and F. (From Heuser and Reese (1981). Reproduced with the permission of *J. Cell Biol.*)

mobilization, little is known about it. Sodium flux seems to be an important factor in the overall process (Birks, 1963) and in many of the intermediate steps. The uptake of choline seems to be linked to the simultaneous entry of sodium (Beach, Vaca and Pilar, 1980; Gundersen, 1980); and so does the activity of choline acetyltransferase (Tucek, 1978) and of mitochondria (Rahamimoff, Lev-Tov and Meiri, 1980). It is not known whether all of the effects of sodium are direct or if some or all of them are mediated through sodium-induced translocation of intracellular calcium or via the activity of one or more ATPase-based transport systems (Birks and Cohen, 1968; Carafoli and Crompton, 1978; Rahamimoff et al., 1978; Rahamimoff, Lev-Tov and Meiri, 1980).

Electrophysiological and morphological observations, together with the results of biochemical studies, lead to the scheme summarized in figure 6 and as follows. The complex molecules used in synthesis and storage of acetylcholine, such as the enzymes, the transport proteins and *new* membrane for vesicles (in contrast to recycled membrane) are made in the cell body and transported through the axon to the nerve terminal (Osborne, 1977; Tucek, 1978). The simple molecules, choline and acetate, are obtained from the environment of the nerve ending, the former by a special system which transports it from the extracellular fluid to the cytoplasm (Vaca and Pilar, 1979); the latter in the form of acetylcoenzyme A from mitochondria. The two substrates react on the enzyme cholineacetyltransferase to form acetylcholine. The newly made acetylcholine is stored in cytoplasm until vesicles are ready to receive it. It is not yet clear how the acetylcholine ion crosses a lipid membrane to enter the vesicle or how it becomes concentrated in vesicles, but recently obtained data suggest that special transport systems may do these jobs (Carpenter and Parsons, 1978; Giompres and Luqmani, 1980; Toll and Howard, 1980; Michaelson and Angel, 1981). A few of the vesicles are new ones delivered from the cell body, but most are made in the nerve ending from materials retrieved from the external membrane of the nerve ending. The newly formed vesicles are coated with filamentous material while they are being made and filled with acetylcholine, but the coating is removed as the completed package is moved into the array of vesicles over an active zone.

The arrival of an action potential in the nerve ending depolarizes it and allows calcium to enter. The calcium causes vesicles to move up to and fuse with the cell membrane, thereby expelling acetylcholine onto the receptors on the shoulders of the postjunctional folds. After releasing its transmitter, the vesicle continues to flatten and

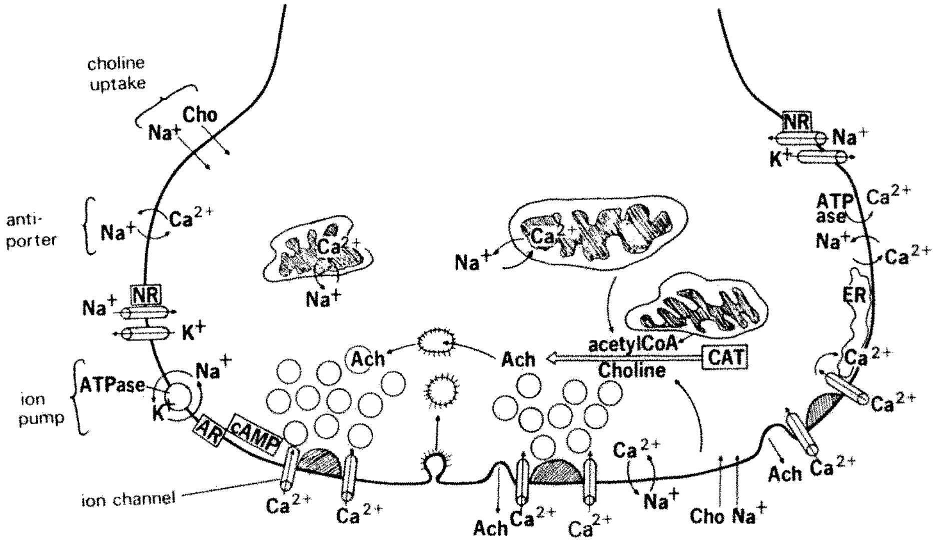

FIG. 6. Scheme of transmitter synthesis, storage and release in motor nerve endings. See text for description. NR = nicotinic receptor; AR = adrenoceptor; CAT = cholineacetyltransferase; ER = endoplasmic reticulum.

meld with the surface membrane. The membrane material moves laterally from the active zone, later to be extracted from the surface and re-used to make new vesicles. The released acetylcholine activates end-plate receptors and is hydrolysed by cholinesterase in the junctional cleft. Some of the choline is taken back into the nerve ending; the rest diffuses away. The calcium in the nerve ending is captured by proteins in the endoplasmic reticulum (Blaustein, Ratzlaff and Kendrick, 1978; Blaustein et al., 1980) and sequestered there or in mitochondria (Alnaes and Rahamimoff, 1975) or possibly in vesicles (Israel et al., 1980; Michaelson et al., 1980) until it is moved out of the nerve by the Na/Ca antiporter or by ATPase (Baker, 1978; Rahamimoff et al., 1980). The sodium that caused the original action potential may diffuse into the cytoplasm to influence intracellular events, but eventually it is removed from the cell by ATPase.

While this description reflects conventional thought, it is not the whole of the matter; much remains to be learned and many observations have not yet been reconciled with the basic scheme. For example, the system just described implies that the acetylcholine of the neuromuscular junction is contained in vesicles and that the cholinoceptors are confined to the shoulders of the junctional folds, but in fact a portion of the acetylcholine is in cytoplasm instead of in vesicles, and there are cholinoceptors on the nerve as well as on the end-plate. These observations illustrate the complexity of the problems to be solved before the mechanism of transmission will be understood. They also indicate some of the controversy the attempts to solve the problem will provoke.

The fact that acetylcholine is in cytoplasm is not surprising, *per se*. Cholineacetyltransferase is a cytoplasmic enzyme (Tucek, 1978), and therefore acetylcholine must go through a cytoplasmic phase before it is incorporated into vesicles. Traditional thinking deals with the non-vesicular acetylcholine as a transition state or as a reserve or store, but this leaves several puzzles unsolved. One relates to the fact that more than one-half of the acetylcholine at neuromuscular junctions is extravesicular (Marchbanks and Israel, 1972; Israel, Dunant and Manaranche, 1979). Miledi, Molenaar and Polak (1980) recently found that a substantial part of the total acetylcholine is in non-neural tissues such as Schwann cells and muscle, but they still estimate that 10–20% of the neural acetylcholine is not in vesicles. This reduces, but does not eliminate, the puzzle: why does a system designed as efficiently as the one outlined in figure 6 allow so much transmitter to be in the cytoplasm where it can be attacked by intracellular cholinesterase (Pilar et al., 1977; Jope, 1981) and apparently wasted?

More troublesome is the fact that non-vesicular acetylcholine is released from the nerve ending. By simultaneously measuring release of transmitter chemically and as reflected by m.e.p.p., Mitchell and Silver (1963) concluded that no more than 2% of the acetylcholine released from unstimulated preparations could correspond to that which produced m.e.p.p. The remaining 98% presumably came from the non-vesicular pool. This observation has been repeated several times, with similar results: at least 98% (Fletcher and Forrester, 1975), and perhaps more than 99.5% (Vizi and Vyskocil, 1979), of the acetylcholine released from a resting nerve ending does not come from vesicles. Approaching the matter another way, Katz and Miledi (1977) and Vyskocil (1979) detected small constant depolarizations of the neuromuscular junction that could be abolished by tubocurarine. They, too, concluded that there is a continuous discharge of non-vesicular acetylcholine at neuromuscular junctions that is many times greater than the spontaneous discharge from vesicles.

It has been reported that the release of non-vesicular material continues during stimulation and that stimulation increases the rate of release (Vizi and Vyskocil, 1979), but Katz and Miledi (1981) were not able to detect a significant contribution of non-vesicular acetylcholine to stimulus-evoked transmission. They speculated that the acetylcholine might be leaking from Schwann cells, muscle or non-synaptic parts of the axon. Acetylcholine is known to be made and released from Schwann cells (Ito and Miledi, 1977), axons (Nachmansohn, 1959) and a variety of non-neural tissues (Shastry and Sadavongvivad, 1978), but its functions in these is not understood.

The release of non-vesicular transmitter from the nerve ending can be viewed as leakage from the reserve or perhaps as some sort of trophic system unrelated to usual neuromuscular transmission, but there are other paradoxes in the acetylcholine storage system. Motor nerves preferentially secrete their most recently synthetized acetylcholine (Potter, 1970), that is they apparently use a "last-in/first-out" inventory system. Were this newly synthetized transmitter stored in vesicles before release, then it must move from cytoplasmic stores directly to the most releasable vesicles, the ones right along the active zone. Yet, this seemingly requires newly-formed vesicles to bypass older vesicles which are lined up ready to be mobilized and released. How can this be? Similarly, experiments with analogues of choline that form "false transmitters" suggest that the newly-formed transmitter is evenly mixed with older material (Whittaker and Luqmani, 1980). This is curious because if transmitter is packaged in vesicles as the scheme in figure 6 suggests, then newly formed transmitter should be in some vesicles and older acetylcholine in others and the contents of the two kinds of vesicles should not mix. Adding to the problem is the evidence that release of non-vesicular acetylcholine is controlled by ATPase (Vizi and Vyskocil, 1979; Vyskocil, 1979), an observation which suggests that the transmitter is not simply leaking out of the nerve.

Moreover, despite the obvious importance of the information, there is not yet agreement on how much acetylcholine is stored in a vesicle. Five thousand molecules per vesicle is the number most commonly cited, but estimates range from 1000 to 60000 (Hubbard, 1973; Kuffler and Yoshikami, 1975; MacIntosh, 1977). There is even controversy over whether the m.e.p.p. is truly the smallest unit of transmission. There are claims (Kriebel, Llados and Matteson, 1976; Matteson, Kriebel and Llados, 1979), disputed by others (Katz and Miledi, 1979; Magleby and Miller, 1981), that the m.e.p.p. may be a composite of four to six smaller "subminiature end-plate potentials".

Some investigators use these and other data to challenge the theory that acetylcholine is released from vesicles (Marchbanks, 1977, 1979; Tauc, 1977, 1979; Van der Kloot, 1977; Israel and Dunant, 1979; Israel, Dunant and Manaranche, 1979). They point out that the basis for the idea is a correlation between the electrophysiological evidence provided by m.e.p.p. and the morphological detection of vesicles and assert that this is not enough to validate the theory.

Those who do not accept the idea that vesicles are the storage sites for transmitter must deal with the m.e.p.p., since there is no doubt that it occurs and little doubt that it shows that transmitter can be released in quanta. Marchbanks (1979) accepts the idea of a quantum, but rejects its association with vesicles. As a possible alternative, he suggests acetylcholine channels. Pointing to the specific channels for the cations sodium, potassium and calcium, he asks why there may not also be a specific channel for the cation acetylcholine. Surely there is a strong electrochemical gradient to drive this ion from the cytoplasm to the extracellular fluid and if there were an ion channel that snaps open and shut, as those for inorganic cations do (Fukushima, 1981), it could pass quantal pulses of acetylcholine to produce m.e.p.p. To deal with the other component of the hypothesis, the structures seen in electron micrographs, he points out that electron microscopes capture an instant and cannot tell which way something is moving in time; the vesicle could be an after-product of transmission instead of a packet of transmitter and he suggests that vesicles might be repositories for calcium taken up during transmission and awaiting extrusion.

Challenges to the quantal hypothesis have not been taken casually (Whittaker, 1979) and some very elegant work is being addressed at the questions raised by the challengers. The results are not fully satisfying. For example, the idea that the vesicles might be part of a scavenging system instead of packets of transmitter has been addressed by attempting to track the vesicles through time before and after stimulation of the nerve. Using the appearance of pits alongside the active bands as indicators of vesicle fusion, and 4-aminopyridine to increase transmitter release, Heuser and Reese (1981) showed clearly that the pits appear after transmission and their numbers are proportional to transmitter released. On the other hand, a critical point is left ambiguous. For some reason, the time-course of pit appearance in electron micrographs (fig. 3) is much slower than the time-course of transmitter discharge as indicated by the end-plate current in similar preparations (fig. 4).

The role of receptors in the nerve ending is equally difficult to establish. The nicotinic cholinoceptor has attracted the most attention. The evidence that motor nerve endings have these cholinoceptors (for reviews see Riker and Okamoto, 1969; Miyamoto, 1977) includes the facts that acetylcholine depolarizes the endings and that its action is antagonized by tubocurarine. This led to the idea that prejunctional cholinoceptors might control acetylcholine release, that is a small amount of acetylcholine is released by the nerve action potential, and refluxes onto the nerve ending to cause the main outpouring (Koelle, 1962). This idea has not fared well. Although acetylcholine depolarizes the nerve ending it causes little or no increase in two major indicators of transmitter release, m.e.p.p. frequency and quantal content (Ciani and Edwards, 1963; Hubbard, Schmidt and Yokoto, 1965). Similarly, while tubocurarine prevents the depolarizing actions of exogenous acetylcholine, it does not cause a significant decrease in m.e.p.p. frequency in unstimulated preparations or of quantal content in preparations stimulated at low frequencies. Thus, the experimental data do not fit with what would be expected if a feedback action of endogenous acetylcholine on nicotinic receptors were a major component of the system that causes the release of the transmitter (Hubbard, Schmidt and Yokoto, 1965; Riker, 1966; Collier and Katz, 1970).

In a variant of this idea, several investigators are considering whether prejunctional muscarinic receptors might influence release of transmitter. The idea receives support from the theory that adrenergic nerves have positive and negative feedback systems controlling release via beta- and alpha-adrenoceptors, respectively (Langer, 1977, 1980; Starke, 1981) and from the evidence that presynaptic nicotinic and muscarinic receptors in the central and parasympathetic nervous systems interact to regulate release of acetylcholine (Szerb, 1977; Kilbinger and Wessler, 1980). Thought along these lines is encouraged by the recent discovery that electric organs of *Torpedo occellata,* which resemble mammalian neuromuscular junctions, contain presynaptic muscarinic receptors (Kloog, Michaelson and Sokolovsky, 1980) that inhibit the release of acetylcholine (Michaelson et al., 1979, 1980), but the data available directly from work on neuromuscular junctions are not yet compelling. The most dramatic effect was reported by Das, Ganguly and Vedasiromoni (1978) who described how oxotremorine, a muscarinic agonist, sharply increased the release of acetylcholine from rat phrenic nerve endings. However, Gundersen and Jenden (1980) could not confirm the observation and neither could Abbs and Joseph (1981). Conversely, a reduction in the m.e.p.p. frequency that can be produced by carbachol and cholinesterase inhibitors has been attributed to a negative feedback effect via muscarinic receptors in the nerve ending (Duncan and Publicover, 1979). The idea is intriguing, but the research is embryonic.

More convincing is the evidence that motor nerve endings contain alpha-adrenoceptors, activation of which can increase the release of transmitter (for review see Bowman and Nott, 1969). Since there are no sympathetic nerves at the neuromuscular junction, and motor nerves are not known to release catecholamines, the physiological function of these receptors is unknown. They apparently are linked to a cyclic nucleotide system in the nerve ending (Bowman and Nott, 1969; Standaert and Dretchen, 1979, 1981) and may serve to modulate transmitter output by increasing calcium flux in times of stress when high concentrations of adrenaline and noradrenaline are circulating in the blood. Something similar may account for the presence of "opiate" receptors (Soteropoulas and Standaert, 1973); they may respond to circulating enkephalins by modulating the function of the nerve ending.

Although it is not yet possible to ascribe a physiological function to prejunctional cholinoceptors, the ionophore associated with the nicotinic one may contribute significantly to the normal function of the nerve ending and to the action of muscle relaxants. Cholinoceptors have several components, one of which recognizes and binds to acetylcholine and another of which causes the cell to respond. In the case of nicotinic cholinoceptors, the latter usually is an ionophore, a protein that can form a channel through which ions cross the cell membrane. Drugs can antagonize acetylcholine either by competing for the recognition site in a classical competitive antagonism, or by blocking the ionophore so that ions cannot flow through its channel.

Riker (1966) demonstrated that intra-arterial injection of acetylcholine produces three phenomena: fasciculations, potentiation of stimulus-evoked contractions and neuromuscular blockage. The first two were shown to be the result of depolarizing actions on the nerve ending. My colleague, Dr Kenneth Dretchen, repeated these observations (fig. 7, top) and then showed that tetrodotoxin prevents the neural effects, but

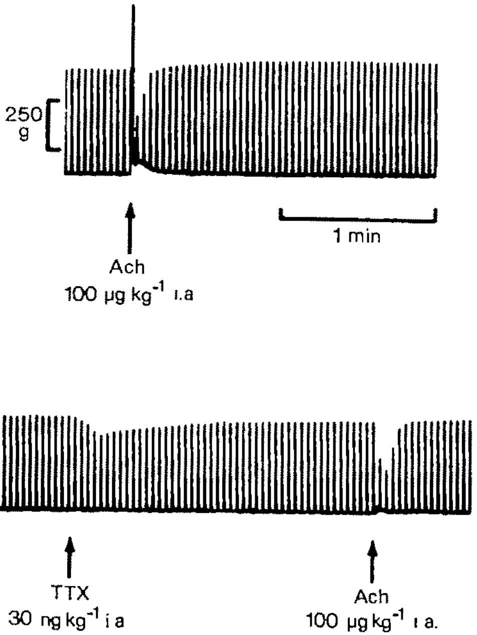

FIG. 7. Effects of acetylcholine, administered i.a. on cat soleus muscle stimulated indirectly once every 2.5 s. Top: control. Bottom: after tetrodotoxin, also administered i.a. (Courtesy of K. Dretchen.)

not the neuromuscular blockage (fig. 7, bottom). Because tetrodotoxin specifically blocks sodium channels, Dretchen's observations presumably mean that the application of acetylcholine to the nerve ending opens a sodium-selective channel. This, in turn, suggests that the ionophore of the nerve ending more closely resembles the acetylcholine-responsive ionophores found throughout the nervous system than it does the one in the muscle end-plate, which passes sodium, potassium, calcium and other cations and is not blocked by tetrodotoxin.

It would not be surprising if the nerve ending contained acetylcholine-sensitive ion channels like those of its parent axon and it would be easy to dismiss the cholinoreceptor/ionophores of the nerve ending as being part of the axon membrane system with no special significance for neuromuscular transmission. However, doing so would overlook the evidence, cited above, that sodium is a key ion in the mobilization of transmitter, and that muscle relaxants interfere with mobilization.

Tubocurarine does not have an obvious prejunctional action in preparations which are resting or are stimulated once every few seconds, but it has strong effects in preparations stimulated at frequencies in the physiological range or above (Lilleheil and Naess, 1961; Standaert, 1964; Ali and Savarese, 1980). Two manifestations of this, the capacity to reduce the muscle's response to tetanic stimulation ("tetanic fade") or to rapidly applied stimuli (e.g. a "train of four"), are so prominent that they are commonly used to gauge the efficacy of tubocurarine in the operating room. This failure of transmission during high frequency stimulation has been ascribed to the nerve's inability to mobilize transmitter rapidly enough to replace that released. According to this reasoning, the output of acetylcholine decreases as stimulation continues and the reduced transmitter is less able to overcome the blockade of postjunctional receptors by tubocurarine. However, this explanation is obsolete. In reality, normal nerve endings are capable of mobilizing transmitter very well; there is little or no decrease in the quantal content of rapidly evoked e.p.p. until tubocurarine is introduced. Then mobilization decreases dramatically (fig. 8)

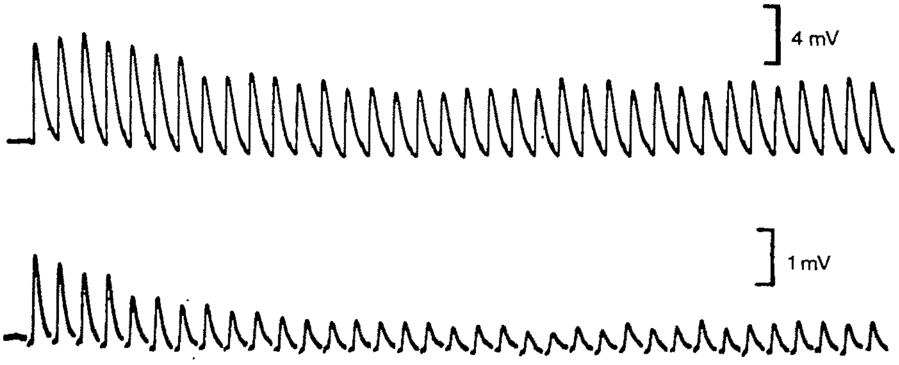

FIG. 8. Effect of repetitive stimulation on end-plate potentials in rat diaphragm stimulated indirectly at 150 Hz. Top: control. Bottom: in the presence of tubocurarine 4×10^{-7} g ml^{-1}. (From Hubbard and Wilson (1973). Reproduced with the permission of *J. Physiol. (Lond.).*)

(Hubbard and Wilson, 1973; Glavinovic, 1979; Magleby, Pallotta and Terrar, 1981).

Bowman (1980) emphasizes that this failure of mobilization must result from an action of the drug on the nerve ending and adds two important observations: the neural cholinoceptors that mediate inhibition of mobilization have a pharmacological profile which is different from those of the end-plate; and, the prejunctional effect is "use dependent". The first is based on his observation that pancuronium, tubocurarine and hexamethonium have different potency ratios in producing tetanic fade and in blocking a single impulse. Hexamethonium is more potent in the former than in the latter, while pancuronium is less potent in the former than the latter and tubocurarine is about equipotent in both. In its response to these antagonists, the nerve ending more closely resembles ganglia than motor end-plates.

Use dependence describes a situation in which a drug does not act until the biological system is used; the rate of onset, rate of offset and intensity of drug effect increase with increasing degree of use. Lignocaine and related local anaesthetics provide an example. They block sodium channels, but only when the channel is activated and opened, apparently because the drug must actually penetrate the channel and plug it (Strichartz, 1976; Ritchie, 1979). Thus lignocaine acts most quickly on nerves which are stimulated rapidly and in which sodium channels are opening most frequently. In the case of the muscle relaxants, Bowman and Webb (1976) and Bowman (1980) studied tetanic fade and inhibition of trains-of-four in comparison with blockade of single stimuli and as a function of how often the nerve was stimulated in the presence of the relaxant. Their results suggest that the prejunctional actions of tubocurarine, pancuronium and Org NC45 are much more use-dependent than the postjunctional actions.

A clue for pulling these observations together is found in the experiments of Ascher, Large and Rang (1979) on the acetylcholine responsive ion channels of ganglia. They showed that, contrary to usual thought, hexamethonium does not compete with acetylcholine for the recognition site of the receptor. Instead it enters and blocks the ion channel opened when acetylcholine binds to its recognition site. Tubocurarine similarly acts in the ion channel instead of by competing with acetylcholine. Since the drugs block only open channels, the blockade is non-competitive, use-dependent and voltage-dependent.

Taken together, these experiments open the possibility that non-depolarizing muscle relaxants reduce the release of transmitter from rapidly stimulated nerve endings because they block open sodium channels and thereby interfere with mobilization. Decamethonium also affects neural sodium channels and mobilization of transmitter, but its actions are more complicated (Blaber, 1970; Ascher, Large and Rang, 1979). Blockade of mobilization would not significantly affect transmission in the usual laboratory setting, where nerves either are not stimulated or are stimulated at slow rates, but it would have important consequences in the living organism where nerves are activated repeatedly. Non-competitive, use-dependent blockade of prejunctional ion channels might account for many of the anomalous, apparently non-competitive, effects of muscle relaxants that are observed in the operating room. Interactions among relaxants and other drugs that may open or block sodium channels also come closer to being understood.

The question of what opens the acetylcholine-sensitive channels in the nerve ending is still unanswered. Bowman (1980) suggested that acetylcholine refluxing from the synaptic cleft is responsible, and that this feedback regulates the mobilization of transmitter. Perhaps this is the case, but acetylcholine-responsive ion channels are found throughout the nervous system, including many places, such as the trunks of unmyelinated nerves and the nodes of Ranvier, which are too remote from synapses to be influenced by released acetylcholine. These channels normally are activated by the action potential and there is no *a priori* reason why those in the nerve ending require a different mechanism. Put another way, the prejunctional nicotinic cholinoceptors may be like the similar receptor-ionophores found on nerve trunks throughout the body in that they respond to acetylcholine by depolarizing the nerve. The physiological relevance of this for axonal conduction is not known (see, however, Nachmansohn, 1959), but the sodium that enters the nerve ending may be essential to the synthesis and release of transmitter, and blockade of this sodium may contribute importantly to the effect of muscle relaxants at junctions activated at physiological frequencies.

These experiments seem to tell us something we did not know about muscle relaxants, but just as importantly they underline how much we have to learn about the release of transmitter from motor nerves. Until now, most work has been done with preparations that were not activated or were activated slowly. From these have come the basic understanding of transmitter release, but the other problem—how transmission is accomplished and maintained in the active organism—has hardly been touched. In early work, drugs were used without appreciation of their complexity, and this impeded understanding of both the physiology and the pharmacology of neuromuscular transmission. These patterns of research are changing; investigators now are studying the dynamics of transmitter release and the complexity of muscle relaxants. Their results are likely to be at least as provocative, of both thought and controversy, as any presented in the past.

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NON-RELAXANT PROPERTIES OF NEUROMUSCULAR BLOCKING DRUGS

W. C. BOWMAN

Theoretically, new compounds with neuromuscular blocking activity might additionally produce almost any type of unwanted pharmacological effect. However, the accumulated knowledge of structure–action relationships in this field is such that medicinal chemists are able to produce effective neuromuscular blocking drugs more predictably, and with less reliance on serendipity, than is the case with any other class of drugs (see, for example, Martin-Smith, 1971). Consequently, most kinds of unwanted activity can be avoided altogether by appropriate molecular design, and any new compounds that do happen to produce unusual unwanted effects can often be discarded at an early stage in preclinical tests. The result is, as experience has taught, that the additional and unwanted actions of neuromuscular blocking drugs mainly (although perhaps not entirely) stem from two characteristic features of the molecules, as pointed out by Paton (1959) more than 20 years ago. One characteristic feature is that the drugs in general use are all organic bases and they might therefore give rise to the rather non-specific effects sometimes produced by such compounds (e.g. histamine release). The other is that, in order to interact with the recognition sites of the cholinoceptors at the neuromuscular junction (i.e. to achieve their desired effect), the drugs must bear some chemical relationship to acetylcholine. Consequently, there is the possibility that they might compete with or mimic acetylcholine at other sites (e.g. cholinesterase, nicotinic autonomic ganglion receptors, and muscarinic receptors). Marshall (1980) has recently reviewed the actions of non-depolarizing neuromuscular blocking drugs at cholinoceptors other than those at the motor end-plate. In the following description actions arising from these two main molecular features are discussed. A few additional actions that as yet cannot be clearly related to particular moieties are also considered.

HISTAMINE RELEASE

Many organic bases (Paton, 1957) can release histamine from tissue mast cells and basophil leucocytes, and most neuromuscular blocking drugs have been shown to produce this effect when sufficiently large doses or concentrations are used (for reviews see Walts, 1975; Maclagan, 1976). The important question, however, is whether the effect is likely to occur with the doses used in anaesthetic practice. All investigators agree that, amongst the commonly used neuromuscular blocking drugs, tubocurarine is the most potent histamine liberator, and signs that could be ascribed to histamine release (urticaria, itching, erythema at the site of injection, hypotension and bronchoconstriction) have sometimes been observed to accompany the use of the drug in human patients. Much more rarely, similar signs have been noted to follow the use of suxamethonium and pancuronium, although in animal tests and human skin tests these two drugs appear to be extremely weak releasers of histamine. Even in the case of tubocurarine, the plasma concentrations that can be shown to increase histamine in normal animals and man are greatly in excess of those necessary to produce neuromuscular block (see *Note added in proof*). It is of course possible, indeed likely, that the plasma concentration of histamine is much smaller than the local concentrations at the sites of release; nevertheless, the role of histamine in the side-effects of tubocurarine remains controversial. A small proportion of patients react to certain neuromuscular blocking drugs with a serious anaphylactoid type of reaction which may or may not involve previous sensitization (Assem, 1977) (for a recent case report in which tubocurarine was the agent responsible, see Baldwin and Churchill, 1979). It seems likely that excessive histamine release does occur in these patients, and it is generally assumed that the greater the propensity of a drug to release

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histamine in normal animals or man, or in *in vitro* tests, the greater the possibility that the drug may give rise to serious idiosyncratic reactions in susceptible individuals. If previous sensitization to the drug is involved, results of tests on normal individuals or tissues will probably be irrelevant.

A combination of the results of a large number of different tests carried out by the authors already quoted in this section, by workers referred to by them, and by Ertama (1978), Booij, Krieg and Crul (1980) and Hughes and Chapple (1981) provide a rough guide to the rank order of potency of various drugs as histamine releasers. Tubocurarine is clearly the most potent and is therefore contraindicated in patients with asthma or in whom there are other reasons to avoid the possibility of histamine release, such as patients with allergic reactions. It may be appropriate to place at the other extreme the compound designated Org NC45, since Booij, Krieg and Crul (1980) found it to be the least effective of the four drugs tested in producing a skin reaction after intradermal injection in human volunteers. They found the rank order of potency to be tubocurarine > metocurine > pancuronium > Org NC45. The results of other workers obtained in different tests suggest that alcuronium, gallamine, suxamethonium and fazadinium should be placed between metocurine and pancuronium (Buckett and Frisk-Holmberg, 1970; Brittain and Tyers, 1973; Ertama, 1978). Atracurium produced signs of histamine release in dogs only in doses eight times greater than the neuromuscular blocking dose (Hughes and Chapple, 1981). Taken together, the results suggest that, unless there is previous sensitization to a particular drug, histamine release may be a problem only with tubocurarine, and even in the case of tubocurarine serious reactions are rare.

CHOLINESTERASE INHIBITION

By virtue of their chemical similarities to acetylcholine, all neuromuscular blocking drugs interact with cholinesterases, but again the important consideration is whether they do this in the concentrations used to produce muscle relaxation. Table I gives the *in vitro* cholinesterase-inhibiting potencies of some neuromuscular blocking drugs.

TABLE I. *Anticholinesterase activities of some neuromuscular blocking drugs (listed in increasing order of potency against acetylcholinesterase). With the exception of those relating to atracurium and fazadinium, the data are from Foldes and co-workers (reviewed in Foldes, 1978 and personal communication) who used erythrocytes as the source of acetylcholinesterase. The data for atracurium and fazadinium are from Hughes and Chapple (1981) who used skeletal muscle as the source of acetylcholinesterase. Since the data for these two drugs were obtained by different workers with a different tissue source of enzyme, they can serve only as a rough guide for comparison in this context.* * *Clinically important*

Drug	Concn (mol litre^{-1}) to produce 50% inhibition	
	Human acetylcholinesterase	Human plasma butyrylcholinesterase
Suxamethonium	1.3×10^{-3}	6.4×10^{-4}
Metocurine	3.2×10^{-3}	4.8×10^{-4}
Pancuronium	3.0×10^{-4}	5.6×10^{-8}*
Gallamine	4.5×10^{-4}	2.4×10^{-4}
Alcuronium	6.7×10^{-4}	5.4×10^{-5}
Tubocurarine	7.2×10^{-4}	3.0×10^{-4}
Decamethonium	3.9×10^{-5}	2.4×10^{-5}
Atracurium	5.6×10^{-5}	not known
Org NC45	6.6×10^{-5}	6.2×10^{-7}
Fazadinium	2.0×10^{-6}	not known
Benzoquinonium	2.2×10^{-7}*	2.1×10^{-5}

The cholinesterase enzymes used to provide the data in table I were human in origin and it is important that this is so, since the enzymes from different species may differ in their substrate and inhibitor specificity (Blaber and Cuthbert, 1962; Hobbiger and Peck, 1969; Hughes, 1972). An additional problem in determining the clinical relevance of any anticholinesterase activity arises from the fact that, in order to produce quantitative and comparable data, the enzyme inhibitor studies must be made *in vitro*. Under these conditions, there is a relative absence of binding sites other than those of the enzyme so that the *in vitro* results may give an overestimate of *in vivo* anticholinesterase activity. It is therefore necessary that *in vitro* evidence of enzyme inhibiting potency be backed up by *in vivo* effects that are characteristic of anticholinesterase activity before it is concluded that cholinesterase inhibition has any importance in practice. Decamethonium provides an illustration of this point; it has a distinct anti-acetylcholinesterase action *in vitro* (Paton and Zaimis, 1949), yet none of its effects *in vivo* can be attributed to enzyme inhibition (Zaimis, 1951).

In practice, of the drugs listed in table I, the anticholinesterase activities of only two are relevant in relation to the extracellular fluid concentrations that produce neuromuscular block. These are the anti-acetylcholinesterase (anti-acetylcholine acetylhydrolase; E.C. 3.1.1.7) action of benzoquinonium (Hoppe, 1951; Bowman, 1958), and the antibutyryl cholinesterase (anti-acetylcholine acylhydrolase; E.C. 3.1.1.8) action of pancuronium (Stovner, Oftedal and Holmboe, 1975).

The acetylcholinesterase inhibiting action of benzoquinonium is a serious disadvantage, not only because of the autonomic side-effects to which it gives rise, but also because it interferes with the effectiveness of anticholinesterase reversal agents such as neostigmine and pyridostigmine. Benzoquinonium produces neuromuscular block of a non-depolarizing nature in spite of its own powerful anticholinesterase activity. However, since it has already inhibited much of the enzyme, anticholinesterase agents have little or no ability to reverse its neuromuscular blocking action. The consequences of the anti-acetylcholinesterase activity of benzoquinonium, which was otherwise a useful relaxant, led to its withdrawal as a neuromuscular blocking drug. A powerful anti-acetylcholinesterase action like that of benzoquinonium would these days be readily observed, and the compound would be discarded after the early screening tests. However, it is also important to exclude compounds with relatively weak but persistent activity of this kind, whether the activity is exerted by the parent drug or by its metabolites, otherwise difficulty with reversal may be unexpectedly experienced after a long-lasting operation in which repeated maintenance doses of the neuromuscular blocking drug have been injected. Drugs that act by increasing the evoked release of acetylcholine from the nerve endings (rather than by inhibiting cholinesterase) are effective antagonists under these circumstances. For example, tetraethylammonium (Blaber and Bowman, 1962), guanidine and 4-aminopyridine are more effective antagonists of benzoquinonium than of tubocurarine. These three antagonists are devoid of anticholinesterase activity and are known to act by increasing transmitter release.

The physiological function, if any, of plasma butyrylcholinesterase is unknown and inhibition of this enzyme by pancuronium is therefore of little consequence in practical terms except in so far as it may impair the metabolism of other drugs, such as procaine and suxamethonium, that are inactivated by this enzyme. Likewise suxamethonium, being a substrate of butyrylcholinesterase, necessarily competes with and inhibits the inactivation of any other substrate (again procaine is an example) of this enzyme. The monoquaternary homologue of pancuronium, Org NC45, is slightly more potent than pancuronium in its neuromuscular blocking action in man, but is less potent in inhibiting plasma cholinesterase. Consequently, its action on this enzyme is even less important in practical terms than that of pancuronium.

It is well known that plasma cholinesterase (acetylcholine acylhydrolase) exists in 10 variants (including one inactive one) controlled by four allelic genes designated E_1^u, E_1^a, E_1^s, E_1^f. The usual genotype is $E_1^u E_1^u$ and it is this usual type that was used for the studies referred to in table I. The genotypes of individuals can be determined by measurement of the so-called dibucaine numbers and fluoride numbers (for a review and description, see Foldes, 1978). Whittaker and Britten (1980) have shown that pancuronium can be used to differentiate the usual ($E_1^u E_1^u$) from the atypical dibucaine-resistant ($E_1^a E_1^a$) enzymes. Pancuronium was about 150 times more effective in inhibiting the normal than the atypical enzyme. In contrast, the monoquaternary homologue Org NC45 had less affinity than pancuronium for the normal enzyme (as indicated also in table I) but greater affinity for the atypical enzyme. The consequence is that Org NC45 was only about five times more effective in inhibiting the normal than the atypical enzyme.

AUTONOMIC GANGLION BLOCKADE

Tubocurarine blocks ganglionic nicotinic receptors (fig. 1) and produces some ganglion block in a dose range similar to that required to produce neuromuscular block. It may have a slightly more powerful action on parasympathetic than on sympathetic ganglia (Guyton and Reeder, 1950). A number of autonomic reflexes arising in the course of surgical operations may be impaired by the ganglion blocking action (Burstein et al., 1950), and this action may contribute to the hypotension (McDowell and Clark, 1969) that can occur in man. The precise role of ganglion blockade in the hypotensive action of tubocurarine is not clear, however, since its ability to release histamine and a possible direct cardiac depressant action (Johnstone, Mahmoud and Mrozinski, 1978) may also contribute.

Fazadinium has been found in animal tests to possess some ganglion blocking activity (Marshall, 1973; Hughes and Chapple, 1976a; Birmingham and Hussain, 1980), and large doses may produce a decrease in arterial pressure in man (Blogg et al., 1973).

Metocurine (trimethyltubocurarine) has only low ganglion blocking potency (Hughes and Chapple, 1976à, b) and does not cause a decrease in arterial pressure in man (Savarese, Ali and Antonio, 1977).

Other neuromuscular blocking drugs in use (gallamine, alcuronium, pancuronium, atracurium, Org NC45) have very little ganglion blocking activity, and ganglion blocking concentrations are not reached in the doses used clinically (Hughes and Chapple, 1981; for reviews see Marshall, 1980; Marshall, Agoston et al., 1980).

Suxamethonium has a weak ganglion stimulant action (Paton, 1959) which appears to be of little practical importance.

INTERACTION WITH MUSCARINIC RECEPTORS

Suxamethonium may occasionally produce a small atropine-sensitive decrease in arterial pressure, which is presumably a consequence of stimulation of muscarinic cholinoceptors (Paton, 1959). This effect is of trivial significance in adults but it may occur more frequently in children. It is unlikely to occur if the patient has received premedication with a drug possessing atropine-like action (e.g. hyoscine or pethidine).

It is obviously preferable that neuromuscular blocking drugs should not block muscarinic receptors, and this type of antagonist activity in the eye, in glands, in the gastrointestinal tract and in the bladder has generally not proved difficult for medicinal chemists to avoid; the neuromuscular blocking drugs in general use have only very weak and unimportant atropine-like actions of this type.

Evidence has accumulated, especially during recent years, that muscarinic receptors are probably not a homogeneous group. By definition, they are all stimulated by muscarine, and they are all blocked by atropine, but they may differ with respect to their interactions with other agonists and antagonists. Figure 1 is a diagrammatic representation of the main components of the autonomic nervous system; the locations of three different subclasses of muscarinic receptors are indicated. For the purposes of the diagram these have been labelled M1, M2 and M3 receptors, but this is not intended to imply a strict classification, since it is almost certainly a gross oversimplification (Birdsall and Hulme, 1976; Birdsall et al., 1979). The first indication that muscarinic receptors may not all be identical in character probably came from the work of Riker and Wescoe (1951) who showed that gallamine,

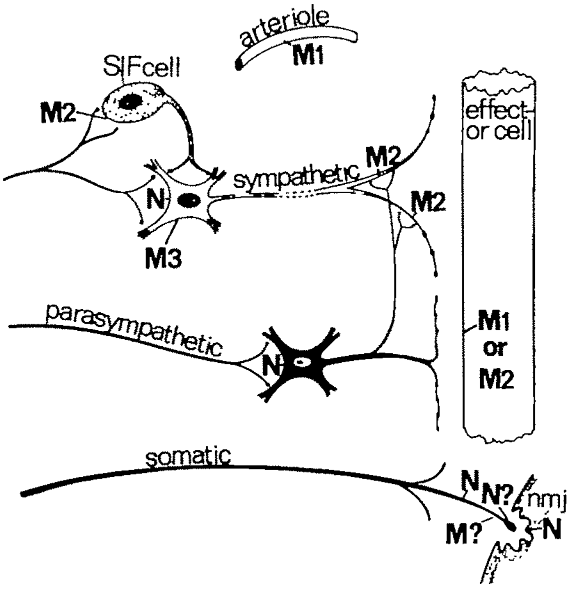

FIG. 1. Diagrammatic representation of the branches of the peripheral nervous system, and some of the postulated sites of muscarinic and nicotinic cholinoceptors. The black nerve fibres are cholinergic, the white postganglionic sympathetic fibre is noradrenergic and the SIF cell is dopaminergic. N = sites of nicotinic cholinoceptors; M = sites of muscarinic cholinoceptors; nmj = neuromuscular junction in skeletal muscle. Arterioles probably do not possess a parasympathetic innervation (with exceptions), but nevertheless possess muscarinic cholinoceptors. Arterioles do possess a sympathetic innervation which is not shown. The muscarinic receptors have been divided into three subclasses (M1, M2 and M3). Most effector cells possess the M1 type, but cardiac cells possess the M2 type. (For further explanation, see text.) There may also be muscarinic and nicotinic receptors present on parasympathetic nerve endings that are involved in feed-back control of transmitter release, but these have not yet been studied in relation to neuromuscular blocking drugs and are not included in the diagram. The muscarinic receptors on somatic nerve endings have not yet been classified (hence the question mark). Nicotinic receptors are also non-homogeneous, but with the exception of the clear difference between ganglionic and motor end-plate nicotinic receptors, the differences with respect to sensitivity to neuromuscular blocking drugs have not been worked out. Somatic motor nerve terminals may possess two types of nicotinic receptors, one of which (N?) may mediate mobilization of transmitter from the reserve to the readily releasable store.

although generally free from atropine-like activity, nevertheless blocked the muscarinic receptors in the cat heart and consequently inactivated the cardiac vagus. In figure 1, the cardiac muscarinic receptors are included in the M2 group to distinguish them from the more usual type labelled M1. Other workers later showed that pancuronium (Saxena and Bonta, 1970), fazadinium (Marshall, 1973), alcuronium (Hughes and Chapple, 1976a), and stercuronium (Li and Mitchelson, 1978) also block the cardiac muscarinic receptors in doses around those required to produce muscle relaxation. On the other hand, tubocurarine, metocurine, Org NC 45 and atracurium block the cardiac muscarinic receptors and other muscarinic receptors only in doses that greatly exceed the neuromuscular blocking doses (Hughes and Chapple, 1976b, 1981; Durant et al., 1979; Marshall, 1980). Figure 2 illustrates an experiment on an anaesthetized cat that demonstrates the specific ability of pancuronium to block the cardiac muscarinic receptors. In this experiment bradycardia was produced either by vagal stimulation or by injection of methacholine (a specific muscarinic receptor stimulant). Pancuronium, in a dose that just caused complete block of the twitches of the tibialis anterior muscle (the effect on the soleus muscle is slightly greater), also caused a pronounced reduction in the bradycardia responses to both methacholine and vagal stimulation. Blockade of this response to methacholine shows that the effect of pancuronium, in the cat at least, is exerted mainly postjunctionally on the cardiac S–A node muscarinic receptors rather than on the vagal nerve endings. The vasodepressor response to methacholine, although blocked by atropine, was not affected by pancuronium, showing that the muscarinic receptors involved (in the arterioles) are not of the same type as those in the S–A node. The arteriolar muscarinic receptors are, on the whole, probably not innervated. Although they may also differ from other muscarinic receptors in that they appear to require the presence of an as yet unknown endothelial factor to mediate vasodilatation (see Furchgott, 1981 for a concise review), they resemble most of the non-cardiac muscarinic receptors in their agonist and antagonist selectivity, and they are therefore labelled M1 in figure 1.

By plotting cumulative dose–response curves for muscle twitch depression and for inhibition of vagally-induced bradycardia from experiments like that of figure 2, the doses that produce 50% block in each case can be determined, and the ratio of these two doses gives a measure of selectivity for the neuromuscular junction. Although satisfactory for the purpose, the measure is not strictly accurate since the two types of dose–response curve are not parallel. This type of experiment in cats has been carried out by several workers including Marshall, Durant, Hughes and Chapple, Savarese, Houston and the author of this article, and many of the results are referred to in Marshall (1980). In the case of gallamine and fazadinium, the ratio is about 1 (i.e. little or no selectivity); for pancuronium and alcuronium it is about 5; for metocurine and atracurium from 15–25; and for Org NC45 about 50 (that is, 50 times as much Org NC45 is required to produce 50% vagal block as to produce 50% muscle twitch block). The ratio obtained is to some extent dependent on experimental details such as frequency of stimulation, and also on the degree of effect chosen for comparison and the species used (Drane and Evans, 1979; Savarese, 1979b). However, if a ratio of 10 or more is obtained in experiments of the type described above on the cat, it can be assumed that, for practical purposes, the drug will be without effect on the cardiac vagus in man. Figure 3 illustrates the absence of effect on the cardiac vagus of doses of Org NC45 and atracurium that were sufficient to produce complete twitch block of a limb muscle. In fact, the doses of both drugs have to be increased considerably beyond this before the cardiac vagus is affected.

The anaesthetized cat lacks spontaneous vagal tone and hence it is necessary to stimulate a vagus nerve, as in the experiments of figures 2 and 3, in order to study any vagal blocking action. It is important to realize, therefore, that when vagal tone is present, as is usually the case in man, a vagal blocking action like that of pancuronium illustrated in figure 2 would result in tachycardia.

Experiments have shown that the cardiac muscarinic receptors are not the only muscarinic receptors that are blocked by certain neuromuscular blocking drugs (at least by gallamine and pancuronium which are the only effective ones so far tested). Stimulation of the vagus has been shown to reduce the release of noradrenaline from concomitantly stimulated sympathetic nerves to the heart (Löffelholz and Muscholl, 1970; Levy

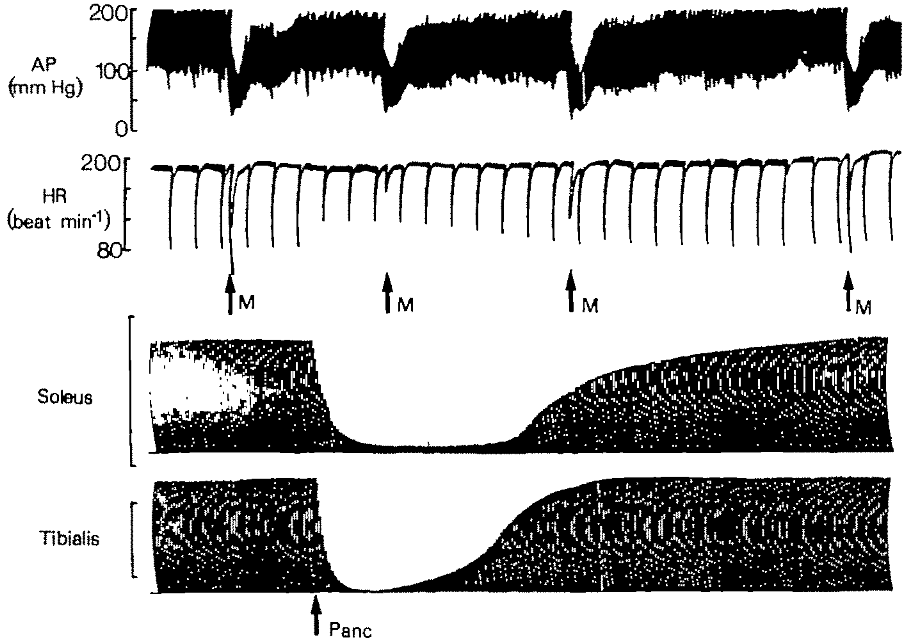

FIG. 2. Cat, chloralose anaesthesia. Records from above downwards: AP = arterial pressure (mm Hg); HR = heart rate (beat min^{-1}); Soleus = maximal twitches of a soleus muscle; Tibialis = maximal twitches of a tibialis anterior muscle (evoked by stimulation of their motor nerves at a frequency of 0.1 Hz). (Muscle twitch tension calibration = 5 N.) The right vagus nerve was stimulated every 100 s for 5 s at 8 Hz to evoke decreases in heart rate. M = i.v. bolus injections of methacholine, each of 10 $\mu g\ kg^{-1}$. Panc = pancuronium 30 $\mu g\ kg^{-1}$ injected. Note that, as well as producing neuromuscular block, pancuronium simultaneously produced a decrease in the bradycardia responses both to vagal stimulation and to methacholine, but it did not affect the depressor response to methacholine. (From an unpublished experiment by J. Houston.)

and Blatberg, 1976; Vanhoutte and Levy, 1980). It is therefore believed that vagal nerve terminals impinge not only upon the nodal and atrial cells of the heart, but also on the sympathetic nerve endings where they act to inhibit the release of noradrenaline. The cholinoceptors on the sympathetic nerve endings are of the muscarinic type (for a brief review, see Shepherd et al., 1978), and there is indirect evidence that they are blocked by gallamine and pancuronium (Vercruysse et al., 1979), but much less effectively by Org NC45 (J. Houston, unpublished observations). Block of these receptors would remove the inhibitory vagal effect, and thus culminate in an increased release of noradrenaline from the cardiac sympathetics. This effect would enhance the tachycardia arising from blockade of the cardiac muscarinic receptors. Because the muscarinic receptors on the sympathetic terminals resemble the cardiac muscarinic receptors in being blocked by gallamine and pancuronium, they have both been labelled "M2" in figure 1, but the evidence of similarity is no stronger than this. There is also evidence that branches of sympathetic nerve endings may end on parasympathetic nerve terminals and act to inhibit the release of acetylcholine therefrom. For the sake of simplicity and because here we are concerned only with cholinoceptors, these sympathetic branches and their associated adrenoceptors are omitted from figure 1.

It is not unlikely that other organs that receive a dual autonomic innervation possess similar reciprocal inhibitory mechanisms, so that stimulation of one branch of the system not only affects the associated organ directly, but also simultaneously inactivates the opposing branch of the nervous system.

Evidence is growing to suggest that somatic motor nerve terminals also possess cholinoceptors (fig. 1), including muscarinic cholinoceptors that mediate an inhibitory modulatory effect on acetylcholine release (Abbs and Joseph, 1981). Block of

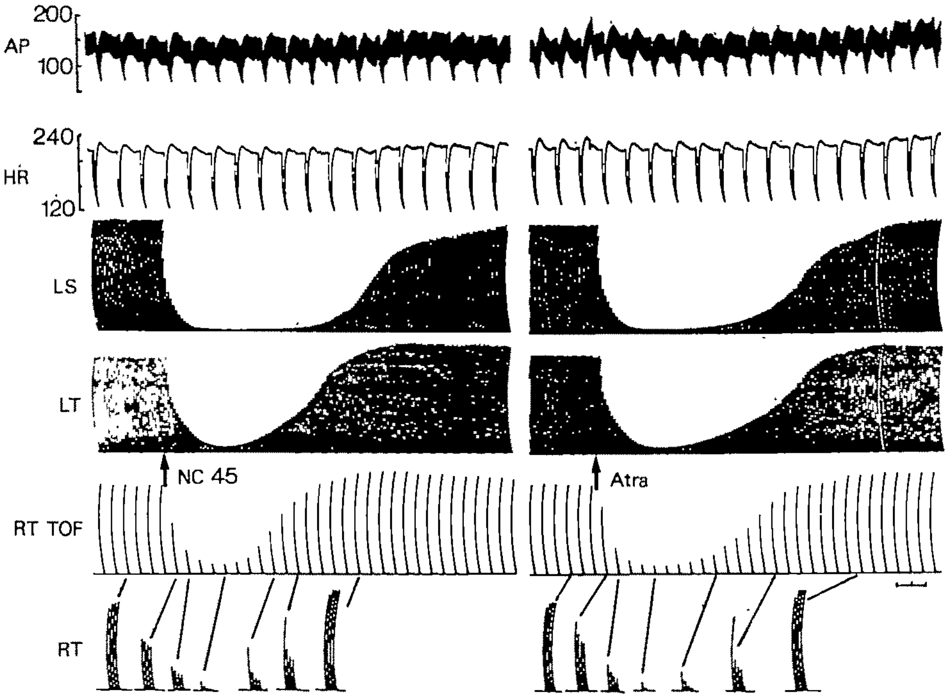

FIG. 3. Cat chloralose anaesthesia. Similar experiment to that of figure 2, but methacholine was not injected. AP = arterial pressure; HR = heart rate (right vagus stimulated for 10 s in every 100 s at 8 Hz); LS = left soleus muscle twitches (0.1 Hz); LT = left tibialis anterior muscle twitches (0.1 Hz); RT TOF = trains-of-four (2 Hz for 2 s every 50 s) recorded from right tibialis anterior; RT = selected trains-of-four from the right tibialis anterior recorded on faster moving paper. Time calibration in min. NC45 = Org NC45 $40\,\mu g\,kg^{-1}$ injected i.v.; Atra = atracurium $200\,\mu g\,kg^{-1}$ injected i.v. One hour elapsed during the gap in the record between the two injections. The two drugs produced essentially similar effects at these doses. Note the absence of cardiovascular changes. (From an unpublished experiment by W. C. Bowman, J. Houston, I. G. Marshall and I. W. Rodger.)

these receptors leads to an increase in evoked acetylcholine release. Although it is not yet known, it is interesting to speculate whether these prejunctional muscarinic receptors could be classified as belonging to the M2 type (in the terms of figure 1), and whether the occasional reports of an increase in acetylcholine release from motor nerve terminals produced by drugs such as gallamine (Galindo and Kelly, 1980) and pancuronium (Gergis et al., 1972) can be related to block of prejunctional muscarinic receptors.

Another location of muscarinic cholinoceptors that are blocked by pancuronium and gallamine, and are therefore indicated as M2 receptors in figure 1, is on the small dopaminergic interneurones (so-called small intensely fluorescent or SIF cells) in sympathetic ganglia. These SIF cells are activated through muscarinic receptors stimulated by acetylcholine that is released from collaterals of the preganglionic cholinergic fibres. Dopamine, released from the SIF cells onto the postganglionic neurones, hyperpolarizes them and therefore suppresses ganglionic transmission (Greengard and Kebabian, 1974). Block of the inhibitory SIF cells by gallamine or pancuronium may, therefore, at appropriate stimulation frequencies, facilitate transmission through the ganglion by inactivating the inhibitory modulating influence of the dopaminergic SIF cell loop (Gardier et al., 1978).

Transmission through sympathetic ganglia is mediated by acetylcholine acting on nicotinic receptors. There are, however, excitatory muscarinic cholinoceptors present on sympathetic ganglia, their physiological function being as yet unknown. These muscarinic receptors are labelled M3 receptors in figure 1. They resemble all other muscarinic receptors in being sensitive to muscarine and to atropine. They differ from those labelled M2 in that they are not blocked by gallamine or pancuronium, and they differ from those labelled M1 (and those labelled M2) in that they are especially sensitive to certain unusual muscarinic agonists such as McN-A-343, AHR-602 and AH6405 (Jones, 1963; Marshall, 1970). Interestingly, these ganglionic excitatory muscarinic cholinoceptors are blocked by mianserin (Kwok and Mitchelson, 1981).

INCREASED NORADRENALINE RELEASE

Block of those prejunctional muscarinic receptors on sympathetic nerve endings that produce a negative modulation of noradrenaline release would increase output in organs that are tonically under the influence of both the sympathetic and the parasympathetic nervous systems (e.g. the heart). Although sympathetic nerve endings in blood vessels possess muscarinic receptors, it is generally considered that on the whole they do not receive a parasympathetic innervation, and some evidence that the vasodilator activity of methacholine is mainly direct rather than being mediated by inhibition of sympathetic tone, is provided by the observation (fig. 2) that pancuronium does not prevent the depressor effect of methacholine (even though it is known that the muscarinic receptors on the sympathetic nerve endings in blood vessels are blocked by pancuronium).

Gallamine causes noradrenaline release in guineapig and cat atria, and in anaesthetized cats by a mechanism that may be quite independent of muscarinic receptor block (Brown and Crout, 1970). Similarly, very large concentrations of pancuronium produce noradrenaline release in isolated guineapig atria under conditions in which parasympathetic block could not be involved (Marshall and Ojewole, 1979).

BLOCK OF NORADRENALINE UPTAKE PROCESSES

Several groups of workers have shown that pancuronium blocks noradrenaline reuptake into sympathetic nerve endings (Uptake 1) both in cardiac muscle and in smooth muscle of guineapigs and rats (Ivankovich et al., 1975; Docherty and McGrath, 1977, 1978; Quintana, 1977; Marshall and Ojewole, 1979; Tomlinson, 1979; Salt, Barnes and Conway, 1980). Fazadinium also produces this effect, but tubocurarine, metocurine and gallamine do not, and Org NC45 is considerably less effective than pancuronium in this respect (Marshall and Ojewole, 1979; Docherty and McGrath, 1980; Marshall, McGrath et al., 1980). Salt, Barnes and Conway (1980) found Org NC45 to be more potent than pancuronium in inhibiting noradrenaline uptake into non-neuronal sites (Uptake 2), but the concentrations of both drugs required for this effect far exceeded those necessary to produce neuromuscular block.

INHIBITORY ACTION ON THE POSTGANGLIONIC CARDIAC VAGUS NERVE

In the cat, at least, the main mechanism through which certain neuromuscular blocking drugs depress cardiac vagal activity is by blocking the postjunctional muscarinic cholinoceptors as described above. This antagonistic action is competitive in nature with low concentrations of antagonist, but may change at high concentrations to become what is called metaffinoid antagonism (Clark and Mitchelson, 1976; Li and Mitchelson, 1978; for review see Marshall, 1980).

From a series of elegant experiments on the isolated guineapig heart, on the other hand, Waud and his coworkers (Lee Son and Waud, 1977, 1978, 1980; Waud, Lee Son and Waud, 1978) have calculated that the concentrations of pancuronium and gallamine that block the responses to postganglionic vagal stimulation are too low to exert significant blocking action on the postjunctional muscarinic receptors, and they conclude (Lee Son and Waud, 1980) that the main site of action of these two drugs in blocking the cardiac vagus is on the postganglionic nerve terminals.

ACTIONS ON THE CARDIOVASCULAR SYSTEM

The haemodynamic effects produced by several neuromuscular blocking drugs have recently been studied in detail in dogs and cats (Booij et al., 1980; Marshall, McGrath et al., 1980). Essentially, their effects were similar to those reported as occurring in anaesthetized man.

The major cardiovascular effects of tubocurarine, as already mentioned, are hypotension with a decrease in systemic vascular resistance, and these effects are largely a consequence of ganglion block. In contrast, gallamine, pancuronium and fazadinium tend to produce tachycardia and hypertension (Kelman and Kennedy, 1970, 1971; Walts, 1975; Hughes, Payne and Sugai, 1976; Frahley, Lemoncelli and Coleman, 1978; Roizen and Freeley, 1978; Pauca and Skovsted, 1981). Peripheral resistance is usually not increased, although Lee, Yang and Lippmann (1980) have described a constrictor effect of pancuronium on veins under some circumstances, and an increase in blood catecholamine concentration after injection of pancuronium in man has been recorded (Nana, Cardan and Domokos, 1973). This last effect must be a potential component of unwanted drug interactions, such as that with imipramine described by Edwards and others (1979).

A combination of the unusual type of atropine-like action, the Uptake 1 blocking action, and the postganglionic cardiac vagal inhibitory action of gallamine, pancuronium and fazadinium amply accounts for the cardiovascular effects of these drugs in man. There is considerable species difference with regard to the relative importance of these effects. For example, block of cardiac muscarinic receptors is readily observed in the cat, whereas Uptake 1 block seems to be the predominant effect in the rat, and block of cardiac vagal nerve endings in the guineapig. It is not known which effect is the most predominant in man, but it is quite likely that the relative importance varies from patient to patient, according to such factors as the pre-existing autonomic balance, the type of premedication given, the anaesthetic used and any concurrent therapy with other drugs. In so far as screening methods are concerned, freedom from cardiac vagal blocking action in the cat, and from other effects on the heart rate and arterial pressure such as is illustrated in figure 3, seems to be a useful indication that a new drug will be free from unwanted cardiovascular effects in man.

BLOCK OF NICOTINIC RECEPTORS

The desired effect of a neuromuscular blocking drug is of course to interact with the postjunctional nicotinic receptors at the motor end-plate, and thereby interrupt transmission. However, stimulation of these receptors by a depolarizing drug such as suxamethonium, and stimulation or block of nicotinic receptors at other sites may lead to effects other than muscle relaxation.

A nicotinic receptor may be regarded as a two-component protein system comprising a recognition site coupled to an ion channel (an ionophore or so-called ion conductance modulator). When an agonist such as acetylcholine binds to the recognition site it causes a conformational change in the associated ionophore with the result that the channel opens and permeability to small cations is increased. Alternatively, or additionally, if the agonist binds to the recognition sites of an already open form of the receptor complex, then it shifts the equilibrium in favour of more open forms. The binding of an antagonist, such as tubocurarine, has the opposite effect; it either prevents channel opening or shifts the equilibrium in favour of the closed forms. The matter is discussed in detail by Dreyer (1982) in this issue. It was originally thought that neuromuscular blocking drugs combined only with the recognition sites of the receptors. However, recent work has shown that tubocurarine and gallamine, and possibly other drugs in this class can, at any rate under certain conditions, also block or plug the open ion channels (Katz and Miledi, 1978; Colquhoun and Sheridan, 1981). It has long been known that depolarizing drugs such as decamethonium, enter muscle fibres at the end-plate region and that this effect is prevented by prior treatment with tubocurarine (Waser and Lüthi, 1957; Taylor et al., 1965; Maclagan and Creese, 1972). Possibly the relatively thin and flexible depolarizing drug molecules pass right through the open ion channels into the myoplasm. At the present time the significance of the effects of neuromuscular blocking drugs on ion channels in relation to the doses used in anaesthetic practice is not known, but the mechanism should be borne in mind as a possible explanation of certain unwanted effects, including interactions with other drugs.

Effects at ganglionic nicotinic receptors have already been referred to, but it is appropriate to consider actions at other nicotinic receptors here.

Prejunctional nicotinic receptors

Figure 1 indicates two hypothetical sites of nicotinic receptors on somatic motor nerve endings, one site being close to the terminals and the other located more centrally at the first node of Ranvier. Stimulation of the former may accelerate mobilization of acetylcholine vesicles from the reserve to the readily-releasable store of transmitter, and be part of a positive feed-back mechanism, activated by the transmitter itself, that functions to maintain acetylcholine output during high frequency stimulation. Arguments supporting such a concept have been put forward (Bowman, 1980). Blockade of such prejunctional cholinoceptors would lead to a rapid fall-off in acetylcholine output during high frequency stimulation, and hence to tetanic fade. Tetanic fade may rightly be considered as part of the relaxation process, and the only point to be made here is that it may differ in prominence with different drugs, according to their relative abilities to block the pre- and postjunctional nicotinic receptors. The fact that different drugs have different abilities to block pre- and postjunctional receptors may account for the observation that certain pairs of neuromuscular blocking drugs (for example, pancuronium with metocurine) produce a greater degree of paralysis than would be forecast from simple additive effects; that is, true potentiation occurs (Lebowitz et al., 1980).

The more centrally situated nicotinic receptors at the first node of Ranvier are thought to mediate depolarization of the axonal membrane (Hubbard, Schmidt and Yokota, 1965). The depolarized region may act as a focus that triggers repetitive firing in the nerve, such as that produced by an anticholinesterase drug. One of the functions of junctional acetylcholinesterase may be to protect the nerve endings at this site from the action of transmitter acetylcholine. Excessive depolarization of this axonal site would block conduction, and hence would abolish evoked acetylcholine release. It is possible that such a prejunctional block of transmitter release contributes to phase II block produced by depolarizing drugs such as suxamethonium. It may also be the explanation for potentiation of non-depolarizing blocking drugs such as Org NC45 by previous administration of suxamethonium (Krieg, Hendricke and Crul, 1981). The receptors supposedly located at the first node of Ranvier have no known physiological function.

Muscle spindles

The motor innervation of the muscle spindles (the gamma efferents) is cholinergic, and the intrafusal fibres are stimulated to contract by acetylcholine acting on nicotinic receptors (Smith, 1963). Block of these receptors when non-depolarizing neuromuscular blocking drugs are administered is unavoidable, and results in reduced sensitivity of the spindles to stretch. As a consequence, the afferent input from the muscles to the brain stem reticular formation is reduced. Since it is the reticular formation's receipt and subsequent processing of sensory stimuli that leads to wakefulness, any reduction in the sensory input will synergize with drugs, such as anaesthetic agents, that act to depress the reticular formation; hence the reported potentiation of general anaesthetics by neuromuscular blocking drugs (Forbes, Cohen and Eger, 1979). This is not the only explanation for the synergism and the matter has been fully discussed in an Editorial by Savarese (1979a). It is unlikely that adequate concentrations of neuromuscular blocking drugs, which are highly polar molecules, could ever penetrate the blood–brain barrier to exert central actions. In any case, when such drugs are administered centrally under experimental conditions, their effects tend to be excitatory rather than depressant.

Depolarizing drugs, such as suxamethonium, produce contraction of the intrafusal fibres of the muscle spindles thereby increasing their sensitivity to stretch. This action probably contributes to the fasciculations produced by suxamethonium.

Other non-relaxant actions of depolarizing drugs

Several non-relaxant effects of these drugs have already been mentioned, and since this class of drugs is typified by suxamethonium, which is described in detail in this issue by Durant and Katz (1982), it is necessary here to make only brief mention of some additional actions for the sake of completeness.

Suxamethonium may increase plasma potassium ion concentration as a consequence of its end-plate depolarizing action, but the effect is normally trivial and unimportant. However, if the chemosensitive area of the muscle fibre membranes has spread as a result of chronic denervation following burns or neurological damage, then a serious hyperkalaemia may accompany the use of suxamethonium.

The depolarizing action of suxamethonium is probably the main factor underlying its propensity to act as a trigger initiating the muscle rigidity and damage in patients susceptible to malignant hyperpyrexia (Denborough, 1980). Similarly, it produces a spastic paralysis rather than a flaccid paralysis in patients suffering from myotonia (Smith, 1976).

Depolarizing drugs, such as suxamethonium, produce a sustained contracture in fibres with multiple innervation, because the chemosensitive area is extensive and the widespread membrane depolarization activates the contractile mechanism directly. In mammals, the extraocular muscles contain fibres with multiple innervation, and the contracture of these muscles produced by suxamethonium is probably responsible for the increase in intraocular pressure that often occurs following administration of this drug (Katz, Eakins and Lord, 1968).

CONCLUSION

The most serious unwanted effects of neuromuscular blocking drugs, especially those in the non-depolarizing group, stem from those actions on the autonomic nervous system that result in changes in cardiovascular control. However, the knowledge of the structure–action relationships gained over the years has now given medicinal chemists the first clues about molecular modifications that may remove even these unwanted effects. Org NC45 and atracurium, with their remarkable lack of effects on the cardiovascular system, are probably examples of the forerunners of a new generation of neuromuscular blocking drugs which will provide anaesthetists with safer and more efficient means of producing muscle relaxation. Animal experiments in this field have proved remarkably effective in detecting useful drugs for further study, and for eliminating and explaining unwanted pharmacodynamic effects. Where animal experiments are unreliable, and will probably continue so to be, is in forecasting the time-course of effect in man, since this is largely a pharmacokinetic problem and only chance could allow the pharmacologist to discover an animal model with pharmacokinetic mechanisms identical with those of man for the particular drug under study. So, while animal studies are essential for picking out potentially useful drugs and for eliminating those with obvious unwanted effects, only subsequent careful clinical studies in patients can determine which drugs have the appropriate time-courses of action to be accepted into anaesthetic practice.

Note added in proof: Since this review was submitted an important paper by Moss and others (*Anesthesiology*, 1981, 55, 19) has been published showing that normal doses of tubocurarine do in fact increase the plasma histamine concentration in man.

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PHARMACOKINETICS OF COMPETITIVE MUSCLE RELAXANTS

R. D. MILLER

Pharmacokinetics refers to the rates of distribution, metabolism and excretion of a drug or its metabolites, or both. Pharmacodynamics, which in essence correlates the blood concentration of a drug with its effects, will be discussed elsewhere in this issue by Professor Hull. The emphasis of a pharmacokinetic approach is on the analysis of the rate and direction of a dynamic process and the dependency of that rate upon other simultaneous processes. The rates are usually expressions of mathematical relationships, and computers are widely used to generate these data.

One of the problems with deriving a more accurate dosage regimen with muscle relaxants and more meaningful interpretation of the magnitude of neuromuscular blockade has been inaccessibility of muscle relaxant concentration at the active site. To help solve this problem, the technique of compartmental analysis has come into use. Feldman (1980), however, argues that making mathematical models to represent the complexities of the human body is seldom worthwhile. Perhaps confusion sometimes arises when one attempts to identify a compartment as an anatomical entity which it may not be. A compartment is defined kinetically as a pool in relationship to a drug concentration–time profile. For example, if a certain fraction of muscle relaxant were lost to some site per unit time, this site would represent a compartment regardless of whether it had anatomical or physiological significance. Thus, the amount of muscle relaxant in a compartment as a function of time can be assessed without knowing where that compartment is physically located.

Some clinicians may be more comfortable with physiologically based models as have been used for the inhaled anaesthetics (Eger, 1964). As described by Stanski (personal communication), these models are limited because large numbers of tissue samples are required for analysis of drug concentration. Furthermore, averages for organ size and blood flow must be assumed. A simpler approach is to characterize drug distribution and elimination using only the dose, plasma concentrations and time. Despite Feldman's (1980) reservations, a pharmacokinetic analysis is extremely important. For example, Katz (1971) has observed a variable response of patients to muscle relaxants. Much of the variability is just not inherent, but can be explained in part by pharmacokinetics. What diseases and physiological changes alter the rate at which the muscle relaxant leaves plasma and is eliminated? What diseases and physiological changes alter the sensitivity of the neuromuscular junction to muscle relaxants? If the answers to these questions were available, muscle relaxant dose could be more precise and much of the "variability" avoided.

ANALYTICAL TECHNIQUES

Until recently, pharmacokinetic data have not been available because analytical methods to measure muscle relaxant concentrations in blood and other body tissues were not available. However, assays for all non-depolarizing muscle relaxants and their antagonists have been developed. Horowitz and Spector (1973) developed a radioimmunoassay method for analysing tubocurarine that was later modified to measure metocurine concentrations in body tissues (Matteo and Khambatta, 1979). This technique had the advantage over the previously developed fluorimetric method because it had a greater sensitivity and did not require extractions from biological fluids. Sensitive and specific assays for neostigmine, pyridostigmine and edrophonium have been developed using high pressure liquid chromatography (De Ruyter, Cronnelly and Castagnoli, 1980). Pancuronium has proven to be a difficult compound to assay. Virtually all the pharmacokinetic studies of pancuronium have used the fluorimetric method

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developed by Kersten, Meijer and Agoston (1973). This method can estimate concentrations greater than 1.5 μg ml^{-1}, but is not specific (Agoston et al., 1973),—that is, the assay does not distinguish between unchanged pancuronium and its metabolites. Thus, when a pharmacokinetic analysis is performed, the investigators do not know the extent to which their plasma concentration reflects the metabolites rather than pancuronium itself. Paanakker and Van de Laar (in preparation) recently developed a high pressure liquid chromatography method to assay pancuronium. This technique is specific, but unfortunately is not especially sensitive. In the last few months in our laboratory, we have developed a mass spectrometry method for pancuronium and vecuronium (Org NC45), a new short-acting, non-depolarizing muscle relaxant. Although this technique is time-consuming and tedious, it is specific in that it will distinguish pancuronium from its metabolites and is sensitive in that it will detect concentrations of 150 pg ml^{-1} or more. Although not directly clinically applicable, the reader should be aware of the problems and limitations of these assays without which a pharmacokinetic analysis would be impossible.

GENERAL PHARMACOKINETICS

Although various mathematical models have been used to characterize the pharmacokinetics of non-depolarizing muscle relaxants, four basic terms can be used to describe the data from these studies. The *elimination half-life* ($T_{\frac{1}{2}}^{\beta}$) simply refers to that time necessary for the plasma concentration of muscle relaxant to decline by one-half during the elimination phase of pharamocokinetics. The *distribution half-life* ($T_{\frac{1}{2}}^{\alpha}$) refers to that time for the plasma concentration of muscle relaxant to decline by one-half during the distribution phase of pharmacokinetics. Although distribution and elimination are initially happening simultaneously, these two half-lives can be determined mathematically. The *volume of distribution at steady state* (V^{ss}) is the sum of the volumes of the central and peripheral compartments. This term approximates the volume to which a muscle relaxant is distributed, although it does not refer to a specific anatomical entity. *Clearance* (*Cl*) refers to the volumes of plasma from which the muscle relaxant is removed per unit time. Knowing the meaning of these terms will allow the reader to understand the clinical importance of just about any pharmacokinetic study of muscle relaxants

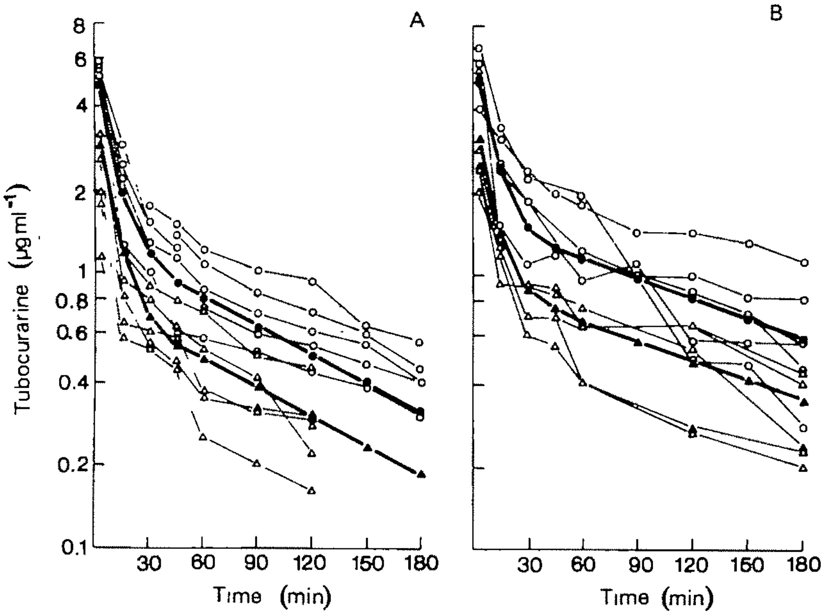

FIG. 1. Plasma concentration *v.* time relationship of tubocurarine in patients with (B) and without (A) renal failure. The solid dark line represents the estimated mean population response for the dose and type of patient (from Sheiner et al., 1979). ○ = 0.5 mg kg^{-1}; △ = 0.3 mg kg^{-1}.

independent of how complicated the mathematics may appear to be.

The rate of disappearance of muscle relaxant from blood is characterized by a rapid initial disappearance which is followed by a slower decay (fig. 1). Distribution to tissues is the major cause of the initial decrease, whereas the slower decay is a result of excretion primarily via the urine and bile (fig. 1). Because muscle relaxants are highly ionized, they do not cross all membranes and have a limited V^{ss}. The initial volume of distribution usually ranges from 80 to 140 ml kg^{-1}, which is not much larger than blood volume. V^{ss} usually ranges from 200 to 450 ml kg^{-1}. This is in contrast to the lipid-soluble, unionized thiopentone which has a V^{ss} of about 2.0 litre kg^{-1}

SPECIFIC PHARMACOKINETIC CONCERNS

Renal failure

Generally, I would use that muscle relaxant which is the least dependent on renal excretion for its elimination when anaesthetizing patients with impaired or absence of renal function. Of the available muscle relaxants, suxamethonium is the only one not dependent on the kidney for its elimination. Although I commonly use suxamethonium in patients with renal failure, it obviously is not suitable for longer cases because of the development of a Phase II block. Of the non-depolarizing muscle relaxants, two short-acting muscle relaxants currently undergoing clinical trials are probably the least dependent on the kidney for their elimination. Only about 15–20% of an injected dose of vecuronium (Org NC45) is eliminated in the urine (unpublished data). Thus the elimination half-life of even large doses (e.g. 0.28 mg kg^{-1}) of vecuronium is only slightly prolonged in patients with no renal function (Fahey et al., 1981). Although not confirmed in man, in rats the major route of vecuronium's elimination appears to be the bile (unpublished data). Another new short-acting muscle relaxant, atracurium (Hunt, Hughes and Payne, 1980), may not depend on the kidney or liver for excretion because of Hoffman elimination, a form of spontaneous breakdown of the quaternary groups dependent on an alkaline pH. However, this route of metabolism of atracurium remains to be proven.

Until these new short-acting muscle relaxants are available, suxamethonium appears to be the muscle relaxant of choice from a pharmacokinetic point of view in patients with renal failure. If one of the currently available non–depolarizing muscle relaxants is to be used, tubocurarine or fazadinium may be preferred to pancuronium, gallamine or metocurine. Meijer and others (1979) found tubocurarine to be less dependent on renal excretion than was metocurine. We believe tubocurarine is also less dependent on renal excretion than is pancuronium (Miller et al., 1977). Once again, this conclusion is tenuous because all studies with pancuronium were performed with the fluorimetric method which does not distinguish unchanged pancuronium from its metabolites. From a practical point of view, the neuromuscular response to non-depolarizing muscle relaxants is especially variable in patients with renal failure. For example, Somogyi, Shanks and Triggs (1977b) found a mean increase in duration of a pancuronium block of 81% in six patients with renal failure compared with patients with normal renal function. However, another four patients had a shortened neuromuscular block. This variability probably reflects the variable cardiovascular and general state of health of patients with renal function. The influence of renal failure also depends on the dose of muscle relaxant used. Even gallamine, which is practically 100% dependent on the kidney for elimination, has been given in small doses in patients undergoing bilateral nephrectomy without a prolonged block (White, de Weerd and Dawson, 1971). Obviously, with small doses, the block can be terminated by redistribution into inactive depots. Because these depots are small in volume, they rapidly become saturated and then primarily urinary excretion becomes the determining factor in the duration of neuromuscular blockade. This means that the margin of safety is enhanced if a drug which is not heavily dependent on the kidney for its elimination is used in patients with renal failure.

Biliary or liver disease

Pancuronium is the only non-depolarizing muscle relaxant which has been extensively studied in patients with biliary or liver disease from a pharmacokinetic point of view. Somogyi, Shanks and Triggs (1977a) found that the neuromuscular blockade and elimination half-life of pancuronium were prolonged in patients with extrahepatic biliary obstruction. Westra, Vermeer and others (1981) later confirmed these observations and attributed the prolonged elimination half-life to an increased volume of distribution. In another study, Westra, Houwertjes and others (1981) also found that an increase in the plasma concentration of bile salts will inhibit hepatic uptake of both vecuronium (Org NC45) and pancuronium. Duvaldestin, Agoston and others (1978) found that, in patients with hepatic cirrhosis, the volume of distribution was increased and the elimination half-life of pancuronium prolonged. Because pancuronium is distributed to a larger volume in patients with cirrhosis, a larger dose of pancuronium may well be required to achieve a given neuromuscular blockade. However, once that neuromuscular blockade had been achieved, it should last longer because elimination is delayed. Monitoring and recording the degree of neuromuscular blockade would determine whether these pharmacokinetic predictions are correct.

Age

Many studies in animals clearly document that neuromuscular junctions degenerate (e.g. increasing degree of denervation) with age, which would alter this pharmacodynamic response to muscle relaxants. Other findings indicate that the pharmacokinetics of muscle relaxants and their antagonists should be altered by ageing (Miller, 1981). Ageing decreases renal function, which may lead to decreased drug elinination and hence increased blood concentrations. Renal perfusion decreases 1.5% per year after maturity; renal blood flow in a 65-year-old patient is half that of a younger patient. This decrease is reflected by a corresponding decrease in glomerular filtration rate and urea clearance. Drug metabolism may be decreased in the elderly because of decreased hepatic concentrations or because of reduced hepatic circulation. Plasma binding of drugs is often decreased in the elderly, thereby giving higher blood concentrations of free (active) drug.

In addition to a reduction in overall weight, the elderly tend to have a decrease in the percentage of total body water and lean body mass and an increase in the percentage of fat. These conditions will decrease distribution volumes and distribution half-life of neuromuscular blocking drugs and their antagonists, which may result in a higher concentration of drug at the neuromuscular junction.

Only one report examines the indications that ageing alters the pharmacokinetics and pharmacodynamics of neuromuscular blocking drugs. McLeod, Hull and Watson (1979) found that ageing decreased the clearance of pancuronium from plasma. Unfortunately, neuromuscular blockade *per se* was not monitored; therefore, a pharmacodynamic analysis could not be performed. Whether the decreased clearance from plasma altered (prolonged) the duration of neuromuscular blockade was not established. More recently, Duvaldestin and colleagues (1980) concluded that, because of this prolonged elimination half-life, elderly patients (75–86 yr) had a duration of neuromuscular blockade from pancuronium nearly twice as long as their younger counterparts (25–55 yr).

At the other end of the age scale, only Fisher and colleagues (1982) have attempted to perform a pharmacokinetic and dynamic analysis of non-depolarizing muscle relaxants, namely tubocurarine, in children. They concluded that neonates and infants have an increased sensitivity (lower blood concentration of tubocurarine to achieve a given neuromuscular blockade) to tubocurarine compared with adult patients. However, because of a larger volume of distribution in neonates and infants, the required initial dose does not vary from that of adults, but, because of a longer elimination half-life, the duration of tubocurarine neuromuscular blockade is probably prolonged.

Hypothermia

In cats, hypothermia was found to prolong both tubocurarine- (Ham, Miller and Benet, 1978) and pancuronium-induced neuromuscular blockade (Miller et al., 1978). Blockades induced by both relaxants are prolonged because of delayed urinary and biliary excretion. With pancuronium, the block may be prolonged also because of decreased metabolism to inactive metabolites (Miller et al., 1978). More recently, Ham and colleagues (1982) found in man that hypothermia had little effect on the pharmacokinetics of tubocurarine. However, their temperature only ranged from a mean of 31.8 °C to 35.8 °C. A larger temperature range, as was used in the animal studies cited above, may have demonstrated a pharmacokinetic dependence on temperature. Despite the apparent lack of influence of hypothermia on the pharmacokinetics of tubocurarine in man, recovery time (25% to 75% recovery of control twitch tension) was prolonged 82% by hypothermia as measured by twitch tension but not by the electromyograph. That mechanical recovery of neuromuscular blockade is prolonged by hypothermia and electrical recovery is not, suggests that neuromuscular transmission *per se* is not significantly affected by hypothermia, at least within the temperature range stated above. These results suggest that hypothermia affects the mechanical properties of the muscle itself. In fact, Ham and others (1982) had one patient who had marked prolongation of tubocurarine neuromuscular blockade which could not be fully antagonized by neostigmine and necessitated mechanical ventilation after operation until body temperature returned towards normal. They also found a tendency for the equilibrium between serum tubocurarine concentration and paralysis to be prolonged by hypothermia. This suggests that hypothermia reduces blood flow to the neuromuscular junction, delaying the onset of paralysis after administration of tubocurarine. However, other than the delayed half-time for equilibrium and differential effect on the twitch tension *v.* electromyograph, a decrease in body temperature to 31.9 °C did not significantly alter the pharamacokinetics of tubocurarine.

Cerebrospinal fluid and anaesthetic requirement

Despite being ionized, non-depolarizing muscle relaxants administered i.v. do pass in the cerebrospinal fluid in amounts which may be clinically significant (Rao and Venkatakrishna-Bhatt, 1975; Matteo, Pua and Khambatta, 1977). Forbes, Cohen and Eger (1979) found that pancuronium administered i.v. reduced halothane anaesthetic requirement by 25%. Whether this was a central effect or was a result of abolition of muscle spindle afferent input was not clarified. The specific correlation between cerebrospinal fluid concentration and anaesthetic effect remains to be established.

Placental transfer

Despite being highly ionized, muscle relaxants clearly cross the placental barrier in small amounts (Poppers and Finster, 1971; Kivalo and Saarikoski, 1976; Duvaldestin, Demetriou et al., 1978). However, these small concentrations have not been shown to have any direct effect on the fetus. Duvaldestin, Demetriou and others (1978) found the cord vein to maternal concentration ratio of pancuronium averaged 0.22, which increased with a greater induction–delivery ratio. The mean cord arterial to cord venous ratio of pancuronium was 0.66 which they felt indicated fetal drug uptake. Nevertheless, all the Apgar scores of the babies were better than 9.

Anaesthetics (table 1)

Despite differing effects on renal and liver function, the choice of general anaesthetic has little or no influence on the pharmacokinetics of tubocurarine. Although this is the only muscle relaxant which has been studied, presumably this conclusion applies to other non-depolarizing muscle relaxants (Stanski et al., 1979, 1980). The ability of inhaled anaesthetics to augment a non-depolarizing neuromuscular blockade is a pharmacodynamic one—that is, the blood concentration of muscle relaxants required to produce paralysis is decreased by inhaled

TABLE I. *Pharmacokinetics of tubocurarine during nitrous oxide–narcotic, halothane and enflurane anaesthesia (mean ± SD) (data taken from Stanski and others (1979, 1980)).* ‡*Endtidal concentrations;* V_1 *= volume of central compartment;* $T_{\frac{1}{2}}Keo$ *= half time for equilibrium between plasma concentration and paralysis. See text for definition of other symbols*

Anaesthetic	No.	$T_{\frac{1}{2}}^{\alpha}$ (min	$T_{\frac{1}{2}}^{\beta}$ (min)	V_1 (litre kg^{-1})	V^{ss} (litre kg^{-1})	Cl (ml kg^{-1} min^{-1})	$T_{\frac{1}{2}}Keo$ (min)
Nitrous oxide–narcotic	14	6.2±3.7	119±66	0.10±0.03	0.30±0.10	2.3±0.7	4.7±1.2
Halothane							
0.5–0.7%‡	7	6.4±2.4	104±56	0.10±0.04	0.29±0.10	2.5±0.6	6.0±1.2
1.0–1.2%‡	7	4.8±3.5	84±69	0.08±0.03	0.30±0.10	2.6±1.0	7.9±2.5
Enflurane 1.3–1.4%‡	7	5.4±2.6	101±48	0.08±0.07	0.25±0.07	2.1±0.3	4.9±1.8

anaesthetics compared with nitrous oxide–narcotic techniques. The only possible pharmacokinetic change was a longer equilibration half-time between plasma concentration and pharmacological effect with halothane *v.* nitrous oxide–narcotic anaesthetic. This probably is because of decreased muscle perfusion with halothane.

Protein binding

The extent to which non-depolarizing muscle relaxants bind to plasma proteins has been widely studied with little agreement. Between 30% and 50% of tubocurarine is bound to albumin and gamma globulin (Ghoneim et al., 1973; Meijer et al., 1979). While pancuronium was originally thought not to be extensively bound to plasma protein, Thompson (1976) found that 87% of pancuronium was bound to gamma globulin and albumin. If so, then only 13% of pancuronium would be unbound and active. The clinical significance of protein binding is unclear. Theoretically, increasing binding would effectively increase the volume of distribution thus reducing free drug available at the site of action. Increased binding might also reduce renal elimination of the drug, since only free drug is filtered at the glomerulus. Thompson (1976) hypothesized that the number of binding sites may remain constant as plasma protein concentration increases if proteins bind with their own binding sites. Furthermore, binding of muscle relaxants with previously mentioned other sites such as cartilage and chondroitin sulphate may be quantitatively and qualitatively as important as plasma protein binding (Olsen, Chan and Riker, 1975; Weitering et al., 1977). Thus, it is difficult to predict the effect of protein binding on muscle relaxant pharmacokinetics. However, protein binding overall should not be of significant clinical concern. Even in patients with renal and hepatic disease, which are diseases well known to have altered protein binding to other drugs, the protein binding of tubocurarine is not altered (Ghoneim et al., 1973).

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PHARMACODYNAMICS OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

C. J. HULL

When a clinical dose of a competitive neuromuscular blocking drug is given i.v. to a patient, a period of latency is followed by a progressive onset of blockade until a maximum is reached after several minutes. Thereafter, the intensity of block declines gradually. The precise relationship between the dose of drug and the time-course of the effect is complex, being dependent upon both pharmacokinetic and pharmacodynamic factors. Following an examination of pharmacokinetic factors (Miller, 1982), this short review considers the relationship between the plasma concentration of drug and the effect.

Numerous studies have sought to elucidate this relationship, using a wide variety of agents and experimental techniques, but controversy still surrounds the mechanism involved (Kopman, 1980; Feldman, 1981; Stanski, 1981). Accepted concepts will be presented first, followed by those which are arguable or simply speculative.

THE AGONIST–RECEPTOR REACTION

According to A. J. Clark's (1933) occupancy hypothesis, an agonist ligand (D) will interact with its receptor site (R) to form bound complexes (DR); and thereby cause an effect (E)

$$D+R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \xrightarrow{k_E} E \qquad (1)$$

The association and dissociation rate constants are k_1 and k_2 respectively. The magnitude of effect is determined by the number of bound complexes, and by a proportionality constant k_E which is referred to as either *efficacy* (Stephenson, 1956) or *intrinsic activity* (Ariens, 1964). According to the law of mass action, the equilibrium equation is:

$$\frac{[D]\,.\,[R]}{[DR]} = \frac{k_2}{k_1} = K_D \qquad (2)$$

where K_D is the equilibrium *dissociation* constant.

If R_T = total concentration of receptors, it follows that

$$[R] = R_T - [DR] \qquad (3)$$

and the proportion of receptor sites occupied (Y_D) is given by

$$Y_D = \frac{[DR]}{R_T} \qquad (4)$$

By substitution of equations (3) and then (4), equation (2) can be developed to:

$$Y_D = \frac{[D]}{[D]+K_D} \qquad (5)$$

Equation (5) can also be expressed as:

$$K_D = \frac{[D](1-Y_D)}{Y_D} \qquad (6)$$

Inspection shows that when $Y_D = 0.5$, $K_D = [D]$. Thus K_D is numerically equal to the free ligand concentration when half the receptor sites are occupied.

If we accept Clark's assumption that effect is proportional to occupancy, then Y_D also yields the fractional effect (expressed as a fraction of the effect when all receptors are occupied by ligand).

The free ligand concentration corresponding to occupancies $Y_D = 0.2$ and $Y_D = 0.8$ can easily be calculated from a further rearrangement of equation (5):

$$[D] = \frac{K_D\,.\,Y_D}{(1-Y_D)} \qquad (7)$$

Thus for $Y_D = 0.2$, $[D]_{0.2} = 0.25K_D$
$Y_D = 0.8$, $[D]_{0.8} = 4K_D$

The concentration for $Y_D = 0.2$ must therefore be increased by a factor of $4/0.25 = 16$ to increase Y_D to 0.8.

The relationships between ligand concentration and occupancy can be expressed graphically by

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direct or semilogarithmic plots. The direct plot (fig. 1A) shows that [DR] (i.e. bound ligand) plotted against [D] (i.e. free ligand) yields a rectangular hyperbola. Thus $[DR] = R_T$ when $[D] = \infty$, and $[D] = K_D$ when $[DR] = 0.5R_T$.

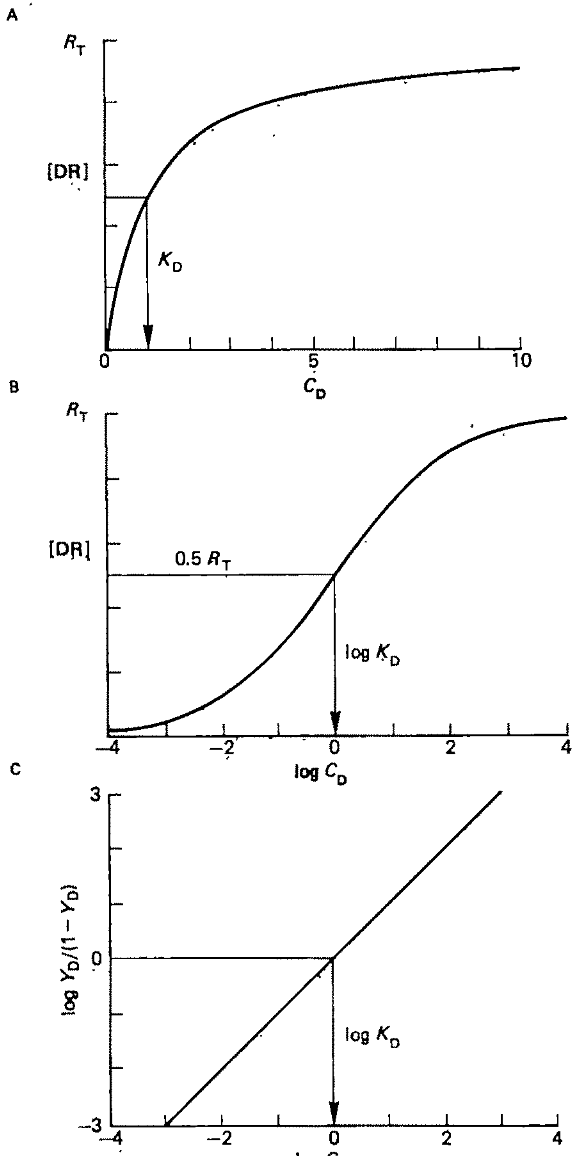

FIG. 1. The relationship between receptor binding [DR] and ligand concentration according to classical occupancy theory. A = linear; B = semilogarithmic; C = Hill. In each case a horizontal line corresponding to $Y_D = 0.5$ is dropped to the X-axis. In the linear plot this indicates K_D, and in the others, $\log K_D$. In each case, $K_D = 1$, since C_D is normalized to multiples of K_D (i.e. $C_D = [D]/K_D$). Following equation (9), the Hill coefficient is 1.

The semilogarithmic* plot yields a sigmoid relationship (fig. 1B). This presentation has the advantage that a greater range of ligand can be accommodated. If the quantity of ligand bound to receptor sites is plotted on the ordinate, the asymptote yields the total number of sites (R_T).

Both these plots have the disadvantage of non-linearity, so that alternative representations are frequently used to linearize the data.

The Hill (1910) plot relates logit Y_D (i.e. $\log[Y_D/(1-Y_D)]$) to $\log[D]$ (fig. 1C). Since Y_D represents fractional occupancy of receptor binding sites, knowledge of R_T (i.e. from a preliminary semilogarithmic plot) is a prerequisite.

Examination of figure 1C shows that the line (of gradient s) intersects the ordinate (i.e. when $\log[D] = 0$) at point $\log Q$, this representing the value of logit Y_D when $\log[D] = 0$. The equation for the line is

$$\log\left(\frac{Y_D}{1-Y_D}\right) = s.\log[D] + \log Q \qquad (8)$$

The relationship between this equation and Clark's occupancy equation (5) can be readily appreciated by rearrangement of (5) and taking logarithms (Norman, 1979):

$$Y_D = \frac{[D]}{[D]+K_D} \quad \text{(equation (5))}$$

becomes

$$\frac{Y_D}{1-Y_D} = \frac{[D]}{K_D}$$

Taking logarithms:

$$\log\left(\frac{Y_D}{1-Y_D}\right) = \log[D] - \log K_D \qquad (9)$$

in the case where $s = 1$, $-\log K_D$ is clearly equal to $\log Q$ (fig. 1), and so equation (8) reduces to equation (9).

Strictly, since K_D is the concentration when $Y_D = 0.5$, and $-\log Q = \log K_D{}^s$, $Q^{-1} = K_D{}^s$. Now, by further rearrangement of equation (8), Y_D can be expressed for any value of s.

$$Y_D = \frac{[D]^s}{K_D{}^s + [D]^s} \qquad (10)$$

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*The prefix log denotes the natural logarithm (base e) throughout this paper.

Generally known as the *Hill coefficient*, s indicates the order of reaction between Y_D and [D], and is of considerable significance (although it will always be 1 in the Clark model). If we follow Clark's assumption that effect is directly proportional to occupancy, then the Hill plot can be constructed in terms of logit E *v.* log [D], where E is the magnitude of the effect expressed as a fraction of the maximum attainable effect (i.e. at $[D] = \infty$). E_{max} is easily determined directly, so does not require preliminary computation. The value of log [D] when logit $E = 0$ yields EC_{50}, the concentration required to produce a 50% effect (i.e. $0.5E_{max}$) (Wagner, 1968).
Thus

$$E = \frac{[D]^s}{EC_{50}{}^s + [D]^s} \tag{11}$$

Equation (11) is directly equivalent to (10) *if* Clark's model is valid.

COMPETITIVE ANTAGONISM

A competitive antagonist (I) will react with free receptor sites, but has no efficacy:

$$I + R \underset{k_4}{\overset{k_3}{\rightleftharpoons}} IR \tag{12}$$

Taking into account the presence of antagonist (Ariens, 1966), the occupancy equation for agonist becomes:

$$Y'_D = \frac{[D]}{K_D(1+[I]/K_I)+[D]} \tag{13}$$

(The prime indicates the presence of a second drug (Mackay, 1966).)

Occupancy equations are more easily expressed with the concentrations expressed as multiples of their respective equilibrium dissociation constants, so

$$C_D = \frac{[D]}{K_D} \quad \text{and} \quad C_I = \frac{[I]}{K_I} \quad \text{(Waud, 1968)}$$

Thus equation (5) becomes

$$Y_D = \frac{C_D}{C_D+1} \tag{14}$$

and equation (13) is simplified to:

$$Y'_D = \frac{C_D}{C_D+C_I+1} \tag{15}$$

Clearly, when negligible antagonist is present, the equation reduces to (14). However, as C_I increases, the concentration of agonist required to maintain the same occupancy increases (i.e. its value of K_D appears to increase). Consequently, the semilogarithmic and Hill plots are displaced to the right (fig. 2). Equation (15) can be expressed in terms of antagonist occupancy:

$$Y'_I = \frac{C_I}{C_I+C_D+1} \tag{16}$$

When negligible agonist $(C = 0)$ is present, equation (16) reduces to

$$Y_I = \frac{C_I}{C_I+1} \tag{17}$$

which is directly equivalent to (14).

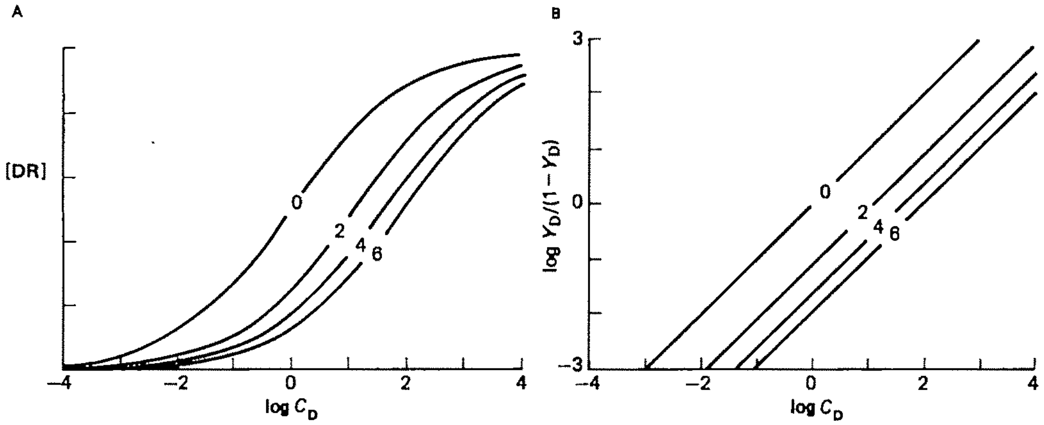

FIG. 2. Figure 1B and C are developed to show the addition of a competitive antagonist in normalized concentrations $C_I = 2$, 4 and 6 (equation (15)). The agonist occupancy curves are shifted to the right, so that at any value of C_D, agonist occupancy is progressively diminished.

Thus the semilogarithmic and Hill representations can be applied to antagonists in the same way as agonists, simply by substituting fractional inhibition (I′) for fractional effect (*E*). However, since fractional inhibition (note the prime) can never be measured in the absence of agonist, the denominator in equation (16) always includes a term representing the presence of agonist. Thus the concentration of antagonist which results in 50% inhibition (EC_{50}) can be readily determined from either semilogarithmic or Hill plots (fig. 3), but *cannot be used to yield an estimate of* K_I.

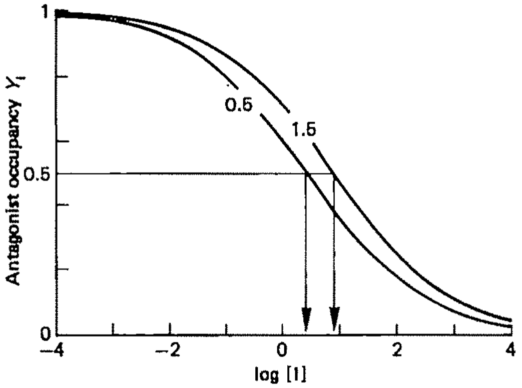

FIG. 3. Occupancy curves for a competitive antagonist (equation (16)) in the presence of agonist in normalized concentrations $C_D = 0.5$ and 1.5. As expected, the antagonist curves are shifted to the right at the higher agonist concentration, so that determination of EC_{50} (arrowed) yields different results. Estimation of K_I by this method (assuming that $EC_{50} = K_I$) is clearly unreliable. These curves are identical with those for fractional reduction in agonist occupancy (Y_D).

Equation (16) also indicates that, in the presence of a constant amount of antagonist, an increase in *agonist* concentration will result in a lower antagonist occupancy Y_I'. Thus equation (12) moves to the left, and some antagonist is "displaced" from binding sites as a new equilibrium is reached.

The rate at which this happens depends upon the association and dissociation *rate* constants for both agonist and antagonist (equations (1) and (12)).

DYNAMICS OF LIGAND–RECEPTOR INTERACTIONS

Up to this point we have considered only the equilibrium condition, ignoring the manner in which equilibrium is *approached*. Many drug receptor reactions are very rapid indeed, making a study of unsteady states somewhat academic, but others are much slower. Indeed, the rate of antagonist–receptor association and dissociation has been claimed (Feldman and Tyrrell, 1970; Feldman, 1981) to be rate-limiting in the onset and offset of effect, so some consideration of the basic principles is worthwhile.

Following early work by Hill (1909), Clark (1926) showed that, when ligand is added to an isolated muscle preparation, the equilibrium of equation (5) is approached exponentially:

$$Y_D = \frac{C_D}{C_D + 1}(1 - e^{-kt}) \tag{18}$$

where $k = k_1[D] + k_2$. (See equation (1).)

The half-time for the association process ($0.693/k$) depends upon both association and dissociation constants (since dissociation begins as soon as some drug is bound) *and* the free ligand concentration. Thus the higher the concentration, the more rapidly is equilibration approached.

If all ligand is instantaneously cleared from the bath, and dissociating ligand is prevented from reassociation by rapid washing, then the dissociation process depends upon k_2 only:

$$Y_D = \frac{C_D}{C_D + 1}(e^{-kt}) \tag{19}$$

where $k = k_2$.

Since K_D is the ratio k_2/k_1 and determines the degree of binding at equilibrium, it gives no clue as to the *rate* of equilibration during either onset or offset. If [D] is known, and k_2 is determined during washout, k_1 can be calculated from the onset data. Early studies made use of this method, and reported that some antagonists dissociated very slowly from receptors. Paton (1961) concluded that atropine dissociated from guineapig ileum with a half-time of 40 min; this undoubtedly gave impetus to the concept that the same might apply to some neuromuscular blocking agents. However, later work (Paton and Rang, 1965; Thron and Waud, 1968) showed that the time taken for atropine to wash out of the tissue was a rate-limiting factor, since the apparent value of k_2 diminished dramatically to 4–5 min when isolated, very thin strips of muscle were used instead of intact gut.

In the situation where the drug is *not* removed instantaneously, the "off" kinetics do *not* follow equation (19), but simply move to a new equilibrium as the biophase concentration changes (Boynaems and Dumont, 1980).

If the ligand concentration changes from initial condition $C_D{}^i$ to a final value of $C_D{}^f$, the occupancy will shift from

$$Y_D{}^i = \frac{C_D{}^i}{C_D{}^i + 1} \quad \text{to} \quad Y_D{}^f = \frac{C_D{}^f}{C_D{}^f + 1}$$

Thus

$$Y_D = Y_D{}^i + (Y_D{}^f - Y_D{}^i).1 - e^{-kt} \qquad (20)$$

where

$$k = k_1[D]^f + k_2 \text{ (as in equation (18)).}$$

In the absence of ligand, the same equations apply to a competitive antagonist.

AGONISM AND ANTAGONISM AT THE CHOLINERGIC RECEPTOR

If Clark's model were to apply, an agonist concentration–effect curve would be hyperbolic (equation (5)), and the corresponding Hill plot should be linear with a slope of 1. Unfortunately, this is simply not the case, since there is abundant evidence (Katz and Thesleff, 1957; Jenkinson, 1960; Rang, 1971) that the acetylcholine concentration/membrane conductance curve is *sigmoid* (fig. 4), yielding a Hill plot of gradient 1.6–1.9 over a wide range of agonists (Changeux and Podleski, 1968). This behaviour (fig. 4) is characteristic of a phenomenon known as *positive co-operativity*, which is defined as a condition in which the order of reaction is greater than 1. It is characterized by:

(1) The ratio $[D]_{0.8}/[D]_{0.2}$ (see equation (7)) is less than 16, so that the effect develops over a narrower range of concentrations than in the Clark model.

(2) The Hill coefficient is greater than 1.

The Hill coefficient is a direct index of co-operativity; hence the utility of this construction. The binding of oxygen to haemoglobin is a classic example of *molecular* co-operativity (Hill, 1910), where binding of one oxygen molecule enhances the affinity for the next, but co-operativity may also be purely phenomenological, with no direct interaction between receptor sites at all.

Thus in the case of the cholinergic receptor we are faced with several possibilities:

(a) As in a model proposed by Hodgkin and Huxley (1952) for the potassium channel in a squid axon, each ionophore may be associated with a number of ligand-binding subunits, some (n) of which must be occupied simultaneously in order to induce a conformational change in the ionophore and thus open the sodium channel.

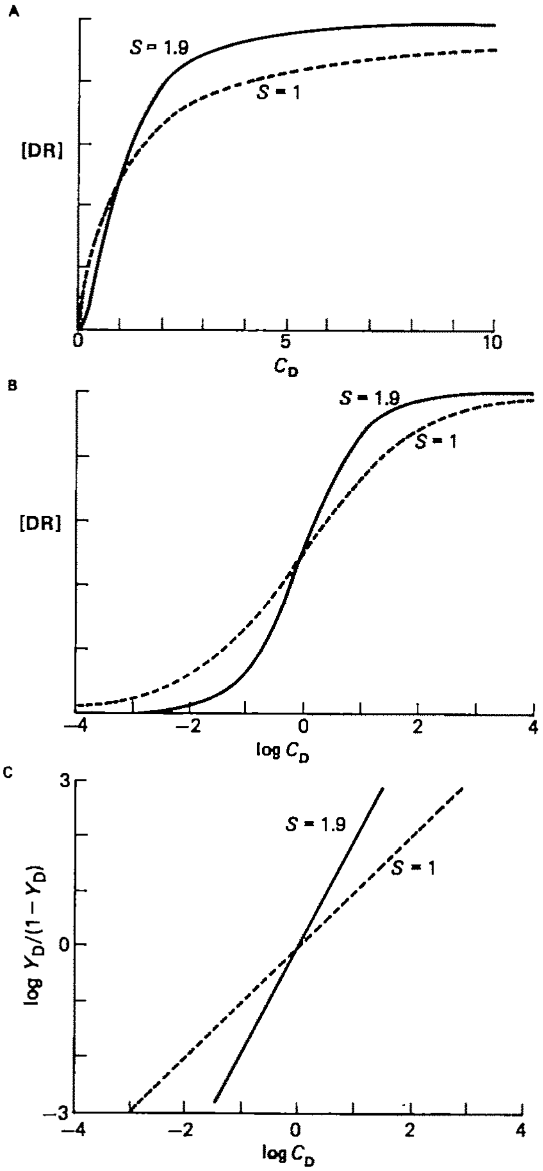

FIG. 4. Agonist co-operativity. To the plots of figure 1 (dotted) are added (solid lines) computed curves for a Hill coefficient (*s*) of 1.9 (equation (10)). The direct plot is no longer hyperbolic, but sigmoid; the semilogarithmic plot has greater sigmoidicity, and the Hill plot gradient has increased from 1 to 1.9.

The relation between effect and concentration is co-operative as a direct result of the multiplicative probability of n simultaneous events, and no interaction between subunits is required. There is a good deal of evidence to support the subunit concept, since each ionophore is surrounded by a "rosette" of apparently identical structures, each of which is likely to possess a ligand binding site (Cartaudl et al., 1978; Rash, Hudson and Ellisman, 1978). However, the probability model insists that the Hill coefficient is equal to n, and must therefore be an integer.

(b) A class of *allosteric* models may be postulated, in which each receptor site can exist in two (or more) *states*, each of which has a different affinity for the ligand (Karlin, 1967).

Thus we can imagine a model consisting of independent subunits, each of which may exist in two conformational states, *closed* (R) with *low* affinity for ligand, in equilibrium with *open* (T) which has *high* affinity. The equilibrium may be presented as:

$$\begin{tikzcd}
\text{channel closed} & & \text{channel open} \\
D+R \arrow[rr, shift left, "K_0"] \arrow[d, shift right] & & T+D \arrow[ll, shift left] \arrow[d, shift right] \\
DR \arrow[u, shift right, "K_{D(R)}"'] & & DT \arrow[u, shift right, "K_{D(T)}"']
\end{tikzcd} \qquad (21)$$

Since the dissociation constant K_0 is large, the majority of units exist in the R state in the absence of ligand. When ligand is added to the system, it binds to both R and T forms in proportion to their affinities. If $K_{D(R)}$ is large, and $K_{D(T)}$ very small, T is consumed to form DT, and the equilibrium $R \leftrightharpoons T$ shifts to the right, thus creating more high affinity sites. Thus the addition of ligand *appears* to have caused a conformational change in the receptor subunit (Colquhoun, 1973).

This added refinement frees the model from the constraint of an integer Hill coefficient.

The model proposed by Monod, Wyman and Changeux (1965) is based on the above principle, but supposes that all subunits change state in a *concerted* fashion, so that each receptor complex can exist in only two states. The intermediate states in which some subunits are "T" and others "R" are thus excluded for the sake of simplicity.

Koshland, Nemethy and Filmer (1966) proposed a *sequential* model, in which no such constraint is imposed, but individual subunits within the "rosette" interact with each other. Thus occupation of one subunit induces a conformational change in its immediate "neighbours" to a higher affinity state. Thus a number of hybrid states can occur, depending upon the geometry of the subunit cluster.

In both the above cases, the Hill coefficient will exceed 1, but the Hill plot itself becomes non-linear, so that equation (11) remains valid only over a narrow range of concentrations.

Identification of one of these proposed models with the cholinergic receptor presents great difficulty, since each can yield saturation curves which closely mimic those obtained experimentally. However, there are some clues. The Hill coefficient does not appear to be an integer. Pre-treatment of the *Electroplax* membrane with dithiothreitol (which reduces disulphide bonds) reduces the Hill coefficient from 1.8 to 1.3, suggesting that the phenomenon of co-operativity is not simply based on occupational probability (Karlin, 1967). More directly, decamethonium in very low concentrations has been shown to reduce the Hill coefficient for carbachol from 1.8 to 1.0 (Changeux and Podleski, 1968), although this finding is open to several interpretations (Podleski, 1973). Recent work has shown that the agonist–receptor interaction involves *several* (probably three) time constants and affinities, thus favouring the concept of an interactive, allosteric model (Giraudat and Changeux, 1981).

Antagonism

If some kind of molecular co-operativity is postulated for the agonist, then competitive antagonism must be considered in those terms. There are three possibilities (Boynaems and Dumont, 1980):

The antagonist

(a) has greater affinity for the "T" configuration. This would *enhance* the agonist at low concentrations before inhibiting it at high concentrations, and agonist co-operativity would be sharply increased.

(b) has greatest affinity for the "R" form. This would exert its effect both by direct site competition *and* by reducing the co-operativity of the agonist.

(c) has no preference for either form. Here, inhibition proceeds according to the classical equation (16), and simply increases the apparent value of K_D.

The author is unaware of evidence that a competitive antagonist may modify the Hill coefficient for acetylcholine, so options (a) and (b) would seem unlikely. If we accept (c), then there is no molecular co-operativity involved in the process of antagonism.

Paton and Waud (1967) showed that in the cat, nearly 80% of receptors must be occupied by tubocurarine before blockade begins, and 90% for complete block. However, this apparent co-operativity can be readily explained by the following evidence: First, each nerve impulse releases much more acetylcholine than is needed to generate the critical degree of end-plate depolarization which triggers an action potential (Paton and Waud, 1967). Second, only a small minority of receptors need be occupied (fig. 5) in order to generate an action potential; the remaining majority constitute "spare receptors" (Ginsborg and Jenkinson, 1976). (N.B. that is not to say that those receptors are truly spare, since that would imply that a maximal increase in membrane conductance could be achieved without them.) The release of excess agonist, and the consequent occupation of more receptors than required, gives the system a "margin of safety" (Paton and Waud, 1967), which ensures that the efficiency of neuromuscular transmission is not impaired by variations in acetylcholine output. Thus a good deal of "antagonism" must take place at receptor level before any macroscopic effect is seen. Since the generation of an action potential is an all-or-none process, the degree of block achieved by each successive level of occupancy is determined by the probability distribution of receptor occupancy by both agonist and antagonist, and by differences in firing threshold over a large population of end-plates.

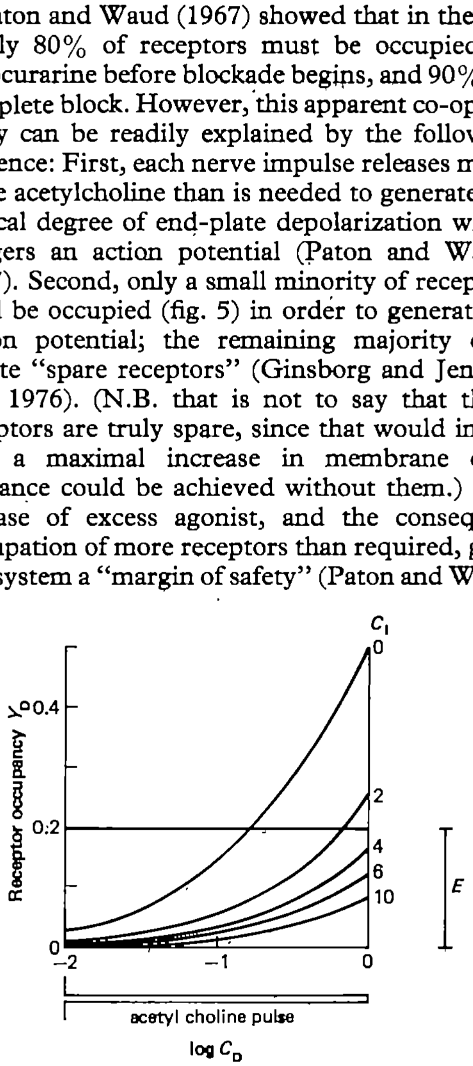

FIG. 5. The margin of safety. The co-operative ($s = 1.9$) agonist occupancy curve of figure 4B is plotted over a limited range (labelled $C_I = 0$), corresponding to an acetylcholine pulse which (say) just reaches an occupancy of 0.5. The effects of increasing normalized concentration of antagonist ($C_I = 2, 4, 6$ and 10) are shown in the lower curves. If an action potential is assumed to follow $Y_D = 0.2$ (horizontal line), then occupancy is considerably in excess of that required. At $C_I = 2$, agonist occupancy is reduced, but is still greater than 0.2. Only when $C_I = 4$, 6 and 10 does Y_D decrease to less than 0.2, and a neuromuscular block develop.

EQUILIBRIUM CHARACTERISTICS OF COMPETITIVE ANTAGONISTS

As the whole binding curve of a classical agonist can be characterized by K_D, so the behaviour of an antagonist can be described by equation (16) if we know K_I (and can thereby calculate the normalized concentration C_I).

K_I can be determined in isolated preparations by the "dose-ratio" method, in which the ratios of antagonist to agonist required to keep a "response" constant over a range of antagonist concentrations are determined. (Since any competitive agonist yields the same result, carbachol is usually preferred to acetylcholine.) The results are plotted on a Schild plot (Arunlakshana and Schild, 1959), from which K_I can be read directly (fig. 6). Table I lists the values of K_I determined by this method for several neuromuscular blocking agents. Results in man are notable by their absence.

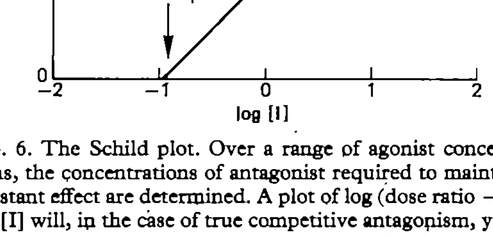

FIG. 6. The Schild plot. Over a range of agonist concentrations, the concentrations of antagonist required to maintain a constant effect are determined. A plot of log (dose ratio − 1) *v.* log [I] will, in the case of true competitive antagonism, yield a linear function of gradient 1. The intercept with the horizontal axis yields log K_I.

TABLE I. *Estimates of K_I by the "dose-ratio" method for different muscle relaxants in the guineapig*

Agent	Species	K_I(nmol)	Author
Tubocurarine	Guineapig (diaphragm)	108	Lu (1970)
Tubocurarine	Guineapig (lumbrical)	110	Waud, Cheng and Waud (1973)
Tubocurarine	Guineapig (lumbrical)	105	Waud (1977)
Pancuronium	Guineapig (lumbrical)	25.1	Waud, Cheng and Waud (1973)
Fazadinium	Guineapig (lumbrical)	377	Waud (1977)

Several authors (Lund and Stovner, 1970; Matteo, Spector and Horowitz, 1974; Agoston et al., 1977) have attempted to estimate K_I by simply determining the plasma concentration of drug at 50% inhibition of twitch height. For this method to be valid, the following conditions must be met: First, the whole kinetic system must be at equilibrium, so that equilibration time constant (i.e. equations (18) and (19), and those for transport to the receptor) do not distort the result. Second, the "free" plasma concentration with which the biophase presumably equilibrates must be determined. This is only possible if the degree of plasma protein binding is measured as part of the study. Finally, the effect of agonist concentration upon the apparent value of K_I must be known. Inspection of equation (16) shows that the presence of agonist is a determinant of antagonist occupancy. It can be argued that when neuromuscular transmission is studied by single twitches at 10-s intervals the antagonist occupancy *between* stimuli is the principal determinant, and that acetylcholine pulses at such long intervals will not disturb the occupancy equation (i.e. C_D is effectively zero): thus equation (16) reduces to:

$$Y_I = \frac{C_I}{C_I + 1} \qquad (22)$$

However, the random release of acetylcholine quanta *between* stimuli makes (22) an unsafe simplification; and it has been shown by Blackman, Gauldie and Milne (1975) that tubocurarine dissociates quickly enough to be significantly displaced *during* the period of a very short ionophoretic pulse of acetylcholine (in the frog). This and other evidence (see below) suggests that

TABLE II. *Estimates of EC_{50} and Hill coefficient (s) for different muscle relaxants in man. Results marked * were not reported, and have been calculated from the experimental results*

Agent	EC_{50} (μg ml^{-1})	*s*	Author
Tubocurarine	0.37	2.53	Sheiner and others (1979)
Tubocurarine	0.45	3.48*	Matteo, Spector and Horowitz (1974)
Pancuronium	0.25	4.18–17	Shanks, Somogyi and Triggs (1979)
Pancuronium	0.113	8.17*	Agoston and others (1977)
Pancuronium (bolus)	0.10	5.63*	Agoston, Feldman and Miller (1979)
(infusion)	0.14	3.63*	
Pancuronium	0.29	7.75	Hull, English and Sibbald (1980)
Fazadinium	1.005	4.46	Hull, English and Sibbald (1980)

confidence in an undisturbed antagonist equilibrium is misplaced, and that the simple "clinical" method may approach the truth only by mutual cancellation of numerous errors (table II).

Variation in the results of different investigators may also be related to the methods used. In particular, variation in stimulus frequency (Ali and Savarese, 1980), the choice of e.m.g. or mechanographic recording, muscle pre-tension (Donlon, Savarese and Ali, 1979) and previous exposure of the preparation to such interfering agents as depolarizing muscle relaxants (Katz, 1971), halogenated anaesthetic agents (Hughes and Payne, 1979), some antibiotics (Sokoll and Gergis, 1981) or even i.v. anaesthetic agents (Kraunak, Pleuvry and Rees, 1977) will have profound effects upon the results obtained. Some investigators (e.g. Payne and Hughes, 1981) have chosen to study the phenomenon of tetanic fade on the grounds that it studies neuromuscular transmission under more physiological conditions than does the single twitch. This is quite true, but almost certainly measures prejunctional as well as postjunctional effects of the neuromuscular blocking agent. Since drugs differ widely in this respect (Williams, Webb and Calvey, 1980), the added complication appears unwelcome to this author.

KINETICS IN THE BIOPHASE

It will be appreciated that a static treatment of the neuromuscular junction is almost meaningless, since the effects of antagonists appear to be determined by the *rates* at which processes occur. The question is: which rates?

For many years Feldman has argued (Feldman and Tyrrell, 1970; Feldman, 1981) on the basis of Paton's (1961) rate theory that the duration of action of a competitive blocking agent is primarily determined by the rate at which it dissociates from the receptor (i.e. up to 1 h or more at *each* receptor site). His argument is founded upon isolated arm experiments in which, after application of a tourniquet, a *small* dose of relaxant was injected to the dorsum of the hand in order to perfuse the muscle by retrograde spread, and after a short delay, the tourniquet released and recovery measured using evoked twitch responses in adductor pollicis. Table III summarizes the results of his and other comparable studies. Since these authors assumed that plasma concentration must be negligible, and receptor–capillary diffusion rapid, slow drug–receptor dissociation was thought to offer the only rational explanation for the observed delay in the recovery of neuromuscular transmission.

TABLE III. *Observed rates of recovery from isolated-arm studies, using different muscle relaxants. In each case, the rate of recovery was calculated from the time taken to recover from 75% to 25% block*

Agent	Rate of recovery (% per min)	Author
Tubocurarine	3.2	Feldman and Tyrrell (1970)
Gallamine	5.2	Feldman and Tyrrell (1970)
Pancuronium	5.0	Agoston, Feldman and Miller (1979)
Fazadinium	5.05	Hashimoto and others (1979)

Feldman and Tyrrell also showed that, after a paralysing dose of tubocurarine, the block in one arm (stimulated with single twitches at 0.2 Hz) recovered more slowly than that in the other (stimulated with tetanic trains of stimuli once per minute). They argued that receptor-bound tubocurarine molecules are displaced by physical bombardment with acetylcholine, so that tetanic stimulation would be expected to accelerate recovery. The results of this experiment were claimed to substantiate the "dissociation theory" for the termination of the effect of tubocurarine.

Waud (1975) suggested that the isolated arm results could be equally well explained by limitation of access of drug to the extracellular space of the muscle (and therefore the biophase), with blood flow being the rate-limiting factor. This explanation was contested by Heneghan and his colleagues (1978), who showed that rate of recovery (in the dog) from paralysing doses of pancuronium was not influenced by large changes in blood flow.

Feldman's assertion that plasma concentration had little to do with the rate of recovery was difficult to reconcile with numerous studies (Matteo, Spector and Horowitz, 1974; Agoston et al., 1977; Shanks, Somogyi and Triggs, 1978) in which recovery of twitch height correlated well with the decline of the logarithm of the plasma concentration. Steady state studies (e.g. Shanks, Somogyi and Triggs, 1978) showed a similar relationship. Other authors (Hull et al., 1978; Sheiner et al., 1979; Hull, English and Sibbald, 1980) have approached the problem by developing pharmacodynamic models which are based upon the concept that the biophase may be visualized mathematically as an elementally small pharmacokinetic compartment the concentration of which will follow (by means of first-order rate constants) that in the plasma, and the Hill transformation between concentration and effect (equation (11)). These authors and others (Shanks, Somogyi and Triggs, 1979) using the same method have shown that after a bolus dose of tubocurarine, pancuronium or fazadinium, plasma concentrations of drug can be fully reconciled with twitch depression throughout the time-course of the drug. This method is not without its difficulties, and Sheiner and others (1979) have been described (with some cause) as having reached "a new zenith of incomprehensibility" (Feldman, 1980). Agoston, Feldman and Miller (1979) later compared the recovery rate after isolated arm experiments with that after a continuous infusion and found that, at 50% recovery, the plasma concentrations in the post-infusion series were about three times greater than those in the isolated arm series. The isolated arm subjects also recovered significantly (four to six times) more rapidly. The results after a bolus dose were intermediate. They interpreted their results as suggesting a compromise theory: *if the plasma concentration decreases very slowly, removal of drug from the synaptic cleft is the limiting factor. If, on the other hand, concentration in plasma decreases abruptly (or is very low to start with), then receptor dissociation is rate-limiting.*

Clearly, clinically based studies could continue for ever without proving anything, since each author's results simply serve to reinforce his own point of view. Other, more direct evidence must be sought regarding the rate-limiting factors, and for this we must return to more fundamental studies on isolated preparations.

The first question is very simple: how fast *do* muscle relaxants associate and dissociate? If we discard the fanciful notion that bound tubocurarine molecules can be displaced wholesale by direct collision with acetylcholine, and retain our belief in the law of mass action, then determination of k_1 and k_2 in equation (20) should resolve the matter.

Waud (1967) attempted to measure these constants in the frog end-plate, but found that, as the experiment refined, the constant appeared to accelerate. He concluded that, although drugs were applied directly to the end-plate by ionophoresis through a micropipette, diffusion to and from the receptors was rate-limiting. Even so, the onset and offset half-times were of the order of a few seconds. He pointed out that the shape of the saturation curves for acetylcholine and tubocurarine would result in much slower onset and offset of effect with the latter. A 20% (approximately) receptor occupancy by an agonist can initiate an action potential. This (fig. 5) can be achieved by a small change in agonist concentration, since the steep part of the occupancy curve is involved and the interaction is co-operative. On the other hand, diffusion of antagonist into the cleft must achieve 80% occupancy before any inhibition of effect is seen, and 90% for full inhibition, because of the agonist's "margin of safety". Thus onset will be delayed despite a high antagonist plasma concentration, and offset takes place along the very flat upper zone of the antagonist occupancy curve (fig. 3), where a large change of concentration must take place to achieve a 10% reduction of occupancy. Waud argued that this change in concentration depends upon the rate of decline in plasma concentration and the rate at which drug is washed out of the muscle.

More recently, Armstrong and Lester (1979) have reported a series of studies on the frog neuromuscular junction, using acetylcholine as the agonist. They found that by positioning a double-barrelled micropipette *very* close to the cleft, recovery after pulses of tubocurarine occurred exponentially with a time constant of 2 s. The onset of inhibition varied with concentration as expected (equation (18)), but was at least 10 times faster. Although rapid, these reactions are very slow compared with the response to acetylcholine pulses (on and off in 20 ms).

To determine whether the "slow" response was a result of receptor binding or of diffusional delay, Armstrong and Lester performed several further experiments:

(1) By the application of cobra α-toxin, which irreversibly occupies receptor sites, a controlled proportion of the receptor population was occluded. Consequently, the recovery time constant increased threefold, suggesting that recovery rate depends upon receptor density.

(2) After collagenase treatment, part of the nerve terminal could be displaced from the post-synaptic membrane. Following this disturbance, end-plate potentials could be produced and inhibited as before, but with the "off" time constant reduced to approximately 0.1 s. This

observation suggests that slow onset and offset are dependent upon the integrity of end-plate architecture.

(3) Over the range 14–29 °C, the "on" and "off" time-constants are only weakly temperature-dependent.

If receptor dissociation were determining the recovery time constant, partial occlusion by a α-toxin and disruption by collagenase would have had no effect, whereas a considerable temperature-dependence would have been expected. The authors concluded that the receptor dissociation rate must have been much faster than the fastest rates observed, with diffusional factors responsible for the difference.

Convincing though Armstrong and Lester's findings might be, acceptance that the receptor rate constants k_3 and k_4 for tubocurarine are very much faster than had previously been supposed raises a new, and equally fundamental question: "If receptor dissociation is not a rate-limiting factor, how can diffusional factors be responsible, since Eccles and Jaeger (1958) estimated that, on a dimensional basis, tubocurarine should diffuse in and out of the cleft with a time constant of *one millisecond*?"

Buffered diffusion

Furchgott (1955) proposed an access-limited *biophase model* in which diffusion to the receptor site played an important part. However, for the sake of simplicity, receptor uptake was assumed to be negligible. Realizing that Furchgott's model could not possibly account for very slow diffusion, as must be the case here, Rang (1966) relaxed Furchgott's "nil-uptake" assumption to form the "limited biophase" model, in which receptor uptake has a profound effect upon biophase concentration. This is particularly applicable to the neuromuscular junction, where the concentration of receptors reaches 3000 per μm^2 on junctional crests (Fertuck and Salpeter, 1974; Rash, Hudson and Ellisman, 1978). Here, where the "diffusion only" time constant is τ_d, the biophase has a volume of V_{bio} μlitre containing a receptor population of R_{bio} mol, the apparent diffusional time constant at low antagonist concentrations becomes

$$\tau_{bio} = (1 + R_{bio}/K_I \, . \, V_{bio})\,\tau_d \qquad (23)$$

Armstrong and Lester estimated that, with likely values substituted into equation (23) ($R_{bio}/V_{bio} = 300$ μmol and $K_I = 0.5$ μmol), τ would increase to about 1 s. This is not surprising when it is appreciated that at 50% occupancy by tubocurarine, only 1 drug molecule in 300 is likely to be free, so that the "apparent" volume of the biophase is 300 times greater (when $I = K_I$) than the anatomical value. At lower concentrations the effect is greater; at higher concentrations, less. Thus at low occupancies, a newly dissociated molecule of antagonist is *much* more likely to recombine with a receptor site for a further period than to diffuse out of the cleft. Equation (23) shows that the apparent diffusion rate is now a function of K_I, since high affinity antagonists will be more "buffered" than low affinity agents with large values of K_I.

The recent findings of Minsaas and Stovner (1980) that the artery-to-muscle onset latencies for pancuronium ($K_I = 25$ nmol), tubocurarine ($K_I = 110$ nmol) and fazadinium ($K_I = 377$ nmol) were 31.9, 21 and 8.6 s respectively would appear to support this hypothesis.

Buffered diffusion explains the difference between receptor interactions on a millisecond timescale and the intact-junction results of Armstrong and Lester. It does not provide a rationale for the slow recovery from an isolated-arm experiment.

In the author's view the arguments for fast dissociation and buffered diffusion are irresistible, so a third question is raised: "If all that is true, how do you explain Feldman's isolated-arm results, which others have confirmed, and the different recovery rates in the two-arm experiment?"

If we accept the concept of buffered diffusion, then the relatively large time-constants which appear to be interposed between plasma concentration and inhibition of effect must be explained. The saturation curve itself may (as suggested by Waud) play a major role, since it intensifies the effect of access-limitation. There must also be an appreciable time lag between capillary and junctional cleft; note the appreciable difference between the results of Waud (1967) and those of Armstrong and Lester (1979) who simply placed their pipette a few microns nearer the end-plate. The role of perfusion must also be considered. Heneghan's study (Heneghan et al., 1978) did not exclude the influence of perfusion, since the rate-limiting factor in his experiment was almost certainly plasma concentration, in which case the negative results were predictable.

Pharmacokinetic factors are also involved, since Feldman's early assumption that after a small (3-mg) dose of tubocurarine into the isolated arm, plasma concentration would be negligible, is simply not tenable. All non-depolarizing agents have small apparent volumes of distribution, so that recirculation after tourniquet release would be expected to yield concentrations which would considerably reduce the concentration gradient between biophase and plasma. The biophase model of Hull, English and Sibbald (1980) for fazadinium predicts that, if the small dose into an isolated arm does not produce a 100% block, the plasma concentration after tourniquet release may actually exceed that in the biophase for a few circulation times, so that drug will diffuse *into* the biophase, and the block will *intensify*. Inspection of the fazadinium study by Hashimoto and his colleagues (1979) shows that this was indeed the case. The tubocurarine study of Feldman and Tyrrell (1970) shows a similar effect, which was not commented upon by those authors.

No significant block of other muscles would be expected, since the plasma concentration, being in its α-decay phase, decays too quickly for biophase concentrations to reach effective values.

Differential recovery from the two-arm experiment can also be explained (Hull, 1980). If dissociation of antagonist from receptors is rapid then, as observed by Blackburn, Gauldie and Milne (1975), a pulse of acetylcholine will (momentarily) increase the "free" drug concentration in the junctional space. Some of this newly dissociated drug will recombine with receptors when the agonist–antagonist equilibrium is restored, but some will diffuse outwards, and enter the diffusional pathway to the local capillary. After a tetanic burst, the same applies, but much more "displacement" of antagonist occurs, and for much longer. Thus diffusion from the cleft is greatly accelerated during the tetanus. If the plasma concentration is lower than that in the cleft, then return is unlikely. Therefore it follows that an arm subjected to tetanic stimuli will recover more rapidly than one subjected only to single twitches. It should be noted that the "displacement" of antagonist is more likely to occur as a result of rapidly shifting equilibria than by physical bombardment.

The different results following isolated arm, bolus and infusion administration (Agoston, Feldman and Miller, 1978) are not unexpected when one considers the differing concentration *gradient* between biophase and plasma in the three cases.

These authors' results are quite in keeping with the behaviour of the pharmacodynamic models of both Hull and Sheiner (except that the isolated arm case cannot be modelled by the latter).

How, then, can we finally relate plasma concentration with neuromuscular blockade? It is evident that receptor occupancy by antagonist is dependent upon passive diffusion from the nearest capillary, although receptor buffering makes this process quite slow. Drug concentration in the peri-capillary e.c.f. will be in close equilibrium with free (i.e. not protein-bound) drug in plasma. pH partition need not be considered since all quaternary ammonium compounds are 100% ionized at pH 7.4. Thus *there is a relationship between plasma concentration and effect at all times*, but that relationship is multifactorial, non-linear and subject to one or more first-order lag-factors (fig. 7). Failure to appreciate the nature of these processes has led some authors to refute the relationship, or propose more unlikely explanations. In order to sustain such arguments it is no longer enough to claim simply that one is right; the elegant experiments of Waud, Armstrong, Lester, Rang and others must be shown to be erroneous.

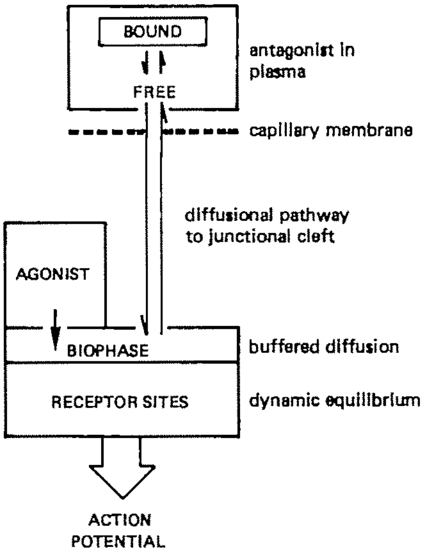

FIG. 7. Factors which influence the relationship between the plasma concentration of a competitive neuromuscular blocking agent and the effect upon neuromuscular transmission. Factors influencing agonism are excluded.

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ANTAGONISM OF NEUROMUSCULAR BLOCKADE

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This review describes developments in the area of antagonist drugs. The discussion will include pharmacokinetics, pharmacodynamics, tests of neuromuscular function, factors affecting antagonism and cardiovascular effects of the antagonists.

In the past, research involving antagonism of neuromuscular blockade has been limited to observing responses following antagonist administration. Variations in the response, in disease states or in different physiological conditions could be recorded, but without knowledge of the influence of drug distribution, metabolism or excretion on the results. New analytical techniques now permit quantitation of antagonist drugs and their metabolites in biological fluids (Chan et al., 1976; Pohlman and Cohan, 1977; Aquilonius et al., 1979; De Ruyter, Cronnelly and Castagnoli, 1980). This information has been coupled with pharmacokinetic analysis to open a new dimension in the investigation of antagonism of neuromuscular blockade.

PHARMACOKINETICS

Normal renal and hepatic function

In the past 5 years, the pharmacokinetics of neostigmine, pyridostigmine and edrophonium have been determined while antagonizing a non-depolarizing neuromuscular blockade in anaesthetized patients (table I) (Calvey, Williams and Muir, 1976; Williams, Calvey and Chan, 1978; Cronnelly et al., 1979; Aquilonius et al., 1979; Cronnelly et al., 1980; Aquilonius et al., 1980; Morris et al., 1981a). A two-compartment open pharmacokinetic model or non-compartmental approach was used to analyse concentrations of these drugs in blood. With the exception of two studies (Calvey, Williams and Muir, 1976; Williams, Calvey and Chan, 1978), blood samples were collected over a 4-h period, allowing better estimates of the elimination phase than a sampling time of 1 h. Measurement of drug concentrations for a period approximately four times the elimination half-life would yield more accurate estimates; however, this is limited by the sensitivity of existing assays.

Neostigmine, pyridostigmine and edrophonium differ little in their pharmacokinetics (table I). The central compartment (V_1) and steady state (V^{SS}) volumes of distribution for these drugs exceed those for plasma, extracellular volumes and the distribution volumes of tubocurarine and pancuronium (Somogyi, Shanks and Triggs, 1977; Meijer et al., 1979). These larger volumes are remarkable since quaternary amines would not be expected to cross lipoid membranes easily and the drugs are not protein-bound. Presumably, extensive tissue localization occurs, resulting in magnification of V_1 and V^{SS} (Kornfeld et al., 1970; Bach and Calvey, 1972a; Cronnelly et al., 1979, 1980; Morris et al., 1981a). In animals, using carbon-14 labelled anticholinesterase drugs, extensive localization was found in liver and kidney (Roberts, Thomas and Wilson, 1965; Birtley et al., 1966; Bach and Calvey, 1972a). However, the distribution volumes are not significantly altered in patients without kidneys (Cronnelly et al., 1979, 1980; Morris et al., 1981b). This suggests hepatic uptake as a major factor contributing to the large distribution volumes of these drugs.

Metabolic clearance

In the absence of renal function, clearance determinations estimate non-renal or metabolic clearance (table II). These estimates are based on the assumption that the metabolic clearance is not affected by the absence of renal function. The fractions of total clearance found to be dependent on metabolism were: neostigmine 50%, pyridostigmine 25% and edrophonium 30% (Cronnelly et al., 1979, 1980; Morris et al., 1981b). In both animals and probably in man, the

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liver is probably the prime site for anticholinesterase metabolism (Roberts, Thomas and Wilson, 1965; Calvey, 1966; Husain et al., 1968).

Analytical techniques allowing sensitive determination and identification of all metabolites of the anticholinesterase drugs are still lacking. Multiple metabolites have been demonstrated for both neostigmine and pyridostigmine, but not all have as yet been identified. In patients with myasthenia gravis and in animals, the primary metabolites for neostigmine, pyridostigmine and edrophonium are 3-hydroxyphenyltrimethylammonium, 3-hydroxy-N-methylpyridinium and edrophonium glucuronide (Roberts, Thomas and Wilson, 1966; Birtley et al., 1966; Husain et al., 1969; Somani et al., 1970; Kornfeld et al., 1970; Bach and Calvey, 1972b). 3-Hydroxyphenyltrimethyl-ammonium has one-tenth the antagonist activity of neostigmine and 1/1000 the activity of anticholinesterase. Edrophonium glucuronide is presumed inactive and no information is available on 3-hydroxy-N-methylpyridinium (Randall, 1950; Hobbiger, 1952; Randall et al., 1955; Barber et al., 1976). With the exception of edrophonium glucuronide, the contribution of metabolites of neostigmine and pyridostigmine to antagonism is unknown. However, if estimates of the fraction of drug metabolized are correct, it is doubtful that active metabolites would contribute significantly.

Renal clearance. Comparison of clearance in the absence of renal function with that in normal patients gives an estimate of the renal excretion of these drugs. Renal excretion accounts for 75% of the clearance of pyridostigmine, 70% of edrophonium and 50% of neostigmine in anaesthetized patients (tables I, II) (Cronnelly et al., 1979, 1980; Morris et al., 1981b). Therefore, in patients without renal function, excretion of these drugs is markedly decreased and their elimination half-lives prolonged.

TABLE I. *Pharmacokinetic variables for anticholinesterase agents in anaesthetized man. †Values listed are means. *Value not reported. **Because of an error in computation, values for Cl, V^{ss} and V_1 listed in Cronnelly and others (1979) should be divided by a factor of 2. Corrected values are listed in the table*

Drug + dose	Route	Anaesthetic	*n*	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	V_1 (litre kg^{-1})	V^{ss} (litre kg^{-1})	*Cl* (ml kg^{-1} min^{-1})	Reference
Neostigmine 5 mg	i.v.	Halothane	5	0.54†	24.2	*	0.09	—	Williams, Calvey and Chan (1978)
5 mg**	i.v.	Halothane	8	3.5	80	0.21	0.7	9.0	Cronnelly and others (1979)
2.5–3 mg	i.v.	N_2O/fentanyl	4	—	53	—	1.08	14.0	Aquilonius and others (1979)
Pyridostigmine 0.35 mg kg^{-1}	i.v.	Halothane	5	6.8	112	0.3	1.1	8.6	Cronnelly and others (1980)
Edrophonium 1.5 µmol kg^{-1}	i.v.	Halothane	5	1.2	33	0.03–0.5	—	—	Calvey, Williams and Muir (1976)
0.5, 1 mg kg^{-1}	i.v.	Halothane	18	7.2	110	0.3	1.1	9.6	Morris and others (1981b)

TABLE II. *Pharmacokinetic variables for anticholinesterase agents in anephric patients. †Values listed are means*

Drug + dose	Route	Anaesthetic	*n*	$T_{\frac{1}{2}}^{\beta}$ (min)	V^{ss} (litre kg^{-1})	*Cl* (ml kg^{-1} min^{-1})	Reference
Neostigmine 0.07 mg kg^{-1}	i.v.	Halothane	4	183†	0.78	3.4	Cronnelly and others (1979)
Pyridostigmine 0.35 mg kg^{-1}	i.v.	Halothane	4	379	1.0	2.1	Cronnelly and others (1980)
Edrophonium 1.0 mg kg^{-1}	i.v.	Halothane	6	206	0.68	2.7	Morris and others (1981b)

The proportion of clearance dependent upon renal mechanisms exceeds that expected for glomerular filtration alone, suggesting the involvement of tubular secretory processes in the clearance of these drugs. High concentrations of neostigmine and pyridostigmine were found in the urine of myasthenic patients in whom the clearance of pyridostigmine exceeded that of creatinine (Nowell, Scott and Wilson, 1962; Kornfeld et al., 1970; Chan and Calvey, 1977). In animals the urinary excretion of neostigmine and pyridostigmine can be blocked by Cyanine 863, an inhibitor of the cationic transport system which is responsible for tubular secretion of basic drugs (Roberts, Thomas and Wilson, 1965; Birtley et al., 1966).

TABLE III. *Pharmacokinetic variables for anticholinesterase agents in renal transplant patients.* †*Values listed are means*

Drug + dose	Route	Anaesthetic	n	$T_{\frac{1}{2}}^{\beta}$ (min)	V^{ss} (litre kg^{-1})	Cl (ml kg^{-1} min^{-1})	Reference
Neostigmine 0.07 mg kg^{-1}	i.v.	Halothane	6	104†	1.0	9.4	Cronnelly and others (1979)
Pyridostigmine 0.35 mg kg^{-1}	i.v.	Halothane	6	83	1.0	10.8	Cronnelly and others (1980)
Edrophonium 1 mg kg^{-1}	i.v.	Halothane	6	87	9.9	0.92	Morris and others (1981b)

Renal failure and kidney transplatation. Renal failure and kidney transplantation are important since the elimination of non-depolarizing muscle relaxants is decreased in the absence of renal function. Studies in patients 1 h after receiving a living related renal transplant have demonstrated that the pharmacokinetics of anticholinesterase drugs are similar to those in patients with normal renal function (Cronnelly et al., 1979, 1980; Morris et al., 1981b) (table III). Similar information has been obtained for tubocurarine in this patient population (Miller et al., 1977). If, however, renal function is severely impaired or absent, the elimination of these drugs is decreased and their half-lives prolonged. The decrease in anticholinesterase clearance from plasma in anephric patients exceeds that reported for pancuronium and tubocurarine (Miller et al., 1977; Somogyi, Shanks and Triggs, 1977; Meijer et al., 1979). Reports of "recurarization" in anephric patients are therefore probably not the result of the muscle relaxant outlasting the antagonist. They may involve an interaction between drugs such as antibiotics or diuretics with residual muscle relaxant activity. Such interactions are not well antagonized by anticholinesterase drugs and could produce muscle weakness in the presence of adequate concentrations of antagonist drugs (Fisk, 1961; Stanley, Giezecke and Jenkins, 1969; Pittinger and Adamson, 1972; Dretchen, Sokoll and Gergis, 1973; Adams and Mathew, 1974; Fogdall and Miller 1974a, b).

PHARMACODYNAMICS

General considerations. Clinically, the magnitude of antagonism appears to be dependent on the amount of recovery of muscle twitch at the time of anticholinesterase administration rather than on the total dose of muscle relaxant given. Onset of antagonism is similarly dependent on the degree of spontaneous recovery (Katz, 1967a, b; Miller, Larson and Way, 1972; Fogdall and Miller, 1973; Ravin, 1975). Edrophonium 10–20 mg was a more effective antagonist when muscle twitch had recovered to 25–75% of control and less effective where spontaneous recovery was only 0–24% of control (Katz, 1967b). However, larger doses of edrophonium (0.5–1.4 mg kg^{-1}) produce adequate and sustained antagonism of neuromuscular blockade from both pancuronium and tubocurarine that had spontaneously recovered to 5–10% of control (Bevan, 1979; Kopman, 1979; Ferguson, Egerszegi and Bevan, 1980; Cronnelly, Morris and Miller, 1982; Morris et al., 1981a). When administered at an approximately equal point during spontaneous recovery, pyridostigmine 10–20 mg or neostigmine 2.5–5 mg completely antagonized the twitch depression induced by pancuronium or tubocurarine (Katz, 1967a, b; McNall et al., 1969; Miller, Larson and Way, 1972; Fogdall and Miller, 1973; Ravin, 1975). Using a cumulative dose technique, pyridostigmine was found to be 5.4–5.8 times less potent than neostigmine as an antagonist (Fogdall and Miller, 1973). In myasthenic patients, the duration of action of pyridostigmine exceeds that of neostigmine and the effects of edrophonium on muscle strength are transient (Osserman, 1955). Physostigmine, an anticholinesterase with a tertiary amine structure, does not have significant antagonist activity up to a dose range exceeding that recommended for treatment of the central anticholinergic syndrome (Baraka, 1978).

In many of the aforementioned studies, anticholinesterase pharmacodynamics were superimposed upon a changing background (spontaneous recovery) of neuromuscular blockade and anaesthetic depth, making the measurement of effect resulting from the antagonist drug alone less accurate.

Potency. Neostigmine, pyridostigmine and edrophonium have been evaluated under conditions of steady state concentrations of halothane anaesthesia and constant infusion of tubocurarine at a rate sufficient to maintain a stable 90% depression of muscle twitch tension (Miller et al., 1974; Cronnelly, Morris and Miller, 1982). Comparing antagonist potency at a dose producing 50% antagonism (ED_{50}), neostigmine was 4.4 times more potent than pyridostigmine and 5.7 times more potent than edrophonium. Since the dose–response curve for edrophonium is not parallel to those of neostigmine and pyridostigmine, the potency ratio is misleading. Potency ratios would vary depending on what point on the dose–response curve the comparisons were made, that is ED_{25}, ED_{50} or ED_{75}. The dose of edrophonium equiantagonistic to the common clinical doses of neostigmine (3 mg/70 kg) and pyridostigmine (15 mg/70 kg) is 0.5 mg kg^{-1}. Since differences in the size of the distribution volumes for neostigmine, pyridostigmine and edrophonium are small, they do not account for differences in potency at equiantagonistic concentrations (Cronnelly et al., 1979, 1980; Morris et al., 1981a) (table I). Affinity of the drugs for the acetylcholinesterase enzyme or other sites of action is probably responsible for determining relative potency (Wilson, Harrison and Ginsburg, 1961).

Onset of antagonism. Beginning from a stable 90% depression of muscle twitch, time to peak antagonism (onset of action) at equiantagonistic doses was shortest for edrophonium and longest for pyridostigmine (table IV). Drug distribution does not account for differences in onset of action since $T_{\frac{1}{2}}^{\alpha}$ for edrophonium (7.2 min) and pyridostigmine (6.8 min) are not different (table I). Differences in affinity for the acetylcholinesterase enzyme or in mechanism of antagonism as suggested by the non-parallel nature of the edrophonium dose–response curve may account for its rapid onset of action (Wilson, Harrison and Ginsburg, 1961; Cronnelly, Morris and Miller, 1982).

Duration of antagonism. Under conditions of stable neuromuscular blockade and anaesthesia the duration of antagonism produced by edrophonium did not differ from neostigmine in equiantagonistic doses (table V) (Miller et al., 1974; Cronnelly, Morris and Miller, 1982). Pyridostigmine had a duration of antagonism approximately 40% longer than edrophonium or neostigmine. At doses of edrophonium (2–4 mg/70 kg) comparable to those used in myasthenia gravis, the duration of antagonism (30–50 min) far exceeds the transient responses observed in myasthenic patients (Osserman, 1955). Although acetylcholinesterase inhibition by low doses of edrophonium may be sufficient to produce transient improvement in muscle strength, it is difficult to explain the duration of antagonism of tubocurarine on this basis, given the reversible nature of this inhibition. Irrespective of mechanism, edrophonium produces effective antagonism of rapid onset and with a duration that is adequate for clinical use.

TABLE IV. *Time to onset of action (min) of edrophonium, neostigmine and pyridostigmine (data from Miller and others (1974) and Cronnelly, Morris and Miller (1982)). †Time to 50% of peak and peak response*

	Edrophonium 0.5 mg kg^{-1}	Neostigmine 3 mg/70 kg	Pyridostigmine 15 mg/70 kg
50%†	0.4±0.1	3.2±0.4	4.0±0.5
Peak†	1.2±0.2	7.1±0.6	12.2±1.8

TABLE V. *Duration (min) of antagonism of edrophonium, neostigmine and pyridostigmine (data from Miller and others (1974) and Cronnelly, Morris and Miller (1982)). †Percentage of peak antagonism during waning effects of edrophonium, neostigmine and pyridostigmine*

	Edrophonium 0.5 mg kg^{-1}	Neostigmine 3 mg/70 kg	Pyridostigmine 15 mg/70 kg
50†	43±5	57±6	83±7
30†	66±7	76±6	130±7

Kinetic–dynamic correlations. Unlike the non-depolarizing muscle relaxants, the relationship between blood concentration of antagonist and the magnitude and duration of antagonism (pharmacodynamics) has not been determined. However, in the non-curarized tibialis anterior muscle of the rat, plasma concentrations of edrophonium were correlated with the facilitation of muscle twitch tension and inhibition of erythrocyte acetylcholinesterase. A similar relationship was present during the return (5–10 min) to control of twitch tension (Barber et al., 1976). Facilitation of neuromuscular transmission by neostigmine and pyridostigmine also correlated with plasma concentration and cholinesterase inhibition; however, this response returned to control values in spite of continued enzyme inhibition. An interesting relationship was also observed between inhibition of rat erythrocyte cholinesterase and facilitation of neuromusclar transmission. When the enzyme was less than 85% inhibited no facilitation occurred, but between 85 and 98%, facilitation was linearly related to enzyme inhibition (Barber, Calvey and Muir, 1979). This suggests a "margin of safety" in enzyme inhibition similar to that seen during blockade of neuromuscular transmission by non-depolarizing muscle relaxants. It may also explain the termination of the pharmacological effect in the face of a significant degree of enzyme inhibition.

In patients with myasthenia gravis a rough correlation (mean $r = 0.6$) was established between plasma concentrations of pyridostigmine and improvement of neuromuscular transmission as measured by electromyography (Chan and Calvey, 1978). At present, the only study in anaesthetized patients found a negative correlation between antagonism of tubocurarine depressed twitch and neostigmine concentrations in plasma or those computed for the peripheral compartment. In addition, no relationship was found to the degree of inhibition of erythrocyte cholinesterase (Calvey et al., 1979). Since neostigmine, pyridostigmine and edrophonium have similar elimination half-lives but pyridostigmine differs in the duration of antagonist action, time-course of antagonism may be unrelated to the clearance of these drugs from plasma. In view of these data, predictions of pharmacodynamic alterations based upon changes in kinetic variables are still speculative.

4-Aminopyridine. Recently, 4-aminopyridine has been used clinically as an antagonist of neuromuscular blockade (Paskov, Stayanov and Micow, 1973). Unlike neostigmine, pyridostigmine and edrophonium, 4-aminopyridine inhibits membrane potassium conductance, rather than the acetylcholinesterase enzyme (Lameignan and Lechat, 1967; Pelhate and Pichon, 1974; Moves and Pichon, 1975; Bowman, Harvey and Marshal, 1976; Vizi, Van Dijk and Foldes, 1977). As a result of this mechanism both spontaneous and neurally-evoked release of acetylcholine from the motor nerve terminal are greatly increased. Compared with neostigmine, 4-aminopyridine provides a longer duration of action, antagonism of antibiotic and local anaesthetic neuromuscular blockade and does not stimulate muscarinic receptors (Matsuo et al., 1978; Miller et al., 1978; Brückner et al., 1980). It also antagonizes ketamine–diazepam anaesthesia (Agoston et al., 1980), respiratory depression from fentanyl (Sia and Zandstra, 1981) and ganglionic blockade from hexamethonium (Durant, Lee and Katz, 1980). Additional clinical uses have been to facilitate neuromuscular transmission in Eaton–Lambert syndrome, botulism and myasthenia gravis (Lundh, Nilsson and Rosen, 1977; Agoston et al., 1978; Ball et al., 1979). In doses smaller than those producing antagonism of neuromuscular blockade, 4-aminopyridine potentiates the effects of neostigmine and pyridostigmine in animals and man (Miller et al., 1978; Miller, Booij and Agoston, 1979). The ED_{50} for neostigmine and pyridostigmine was reduced by 68% and 75%, respectively, when combined with a dose of 4-aminopyridine which produced no antagonism by itself. The time to peak effect (onset of action) was slower for both neostigmine and pyridostigmine, but only neostigmine was prolonged in duration by combination with 4-aminopyridine. Although more time would be required for complete antagonism, the amount of atropine required to prevent bradycardia was reduced (60–70%) by combining 4-aminopyridine with neostigmine. This may prove advantageous in terms of haemodynamic stability. The cardiovascular effects of 4-aminopyridine alone have been studied in animals and patients with botulism (Ball et al., 1979; Bowman et al., 1981). Increases in heart rate and arterial pressure were noted, probably as a result of facilitation of sympathetic nervous system activity. These changes in addition to central nervous system stimulant properties may severely limit the routine use of 4-aminopyridine as an antagonist of neuromuscular blockade (Booij, 1980).

What controls antagonism? Irrespective of the mechanism of antagonism, the rate for dissociation of relaxant–receptor complex and the relaxant concentration gradient between receptor and blood may control the recovery of neuromuscular function following administration of the antagonist. Several studies have addressed this issue. In one, neostigmine was unable to antagonize a tubocurarine blockade until plasma concentrations of tubocurarine decreased to less than 1 $\mu g\,ml^{-1}$ and spontaneous recovery was occurring (Baraka, 1967). These results were interpreted to suggest that, since a favourable concentration gradient from receptor compartment to blood was not present, reversal did not occur (Feldman and Agoston, 1980). Also, in a small number of patients neostigmine failed to modify the development of a neuromuscular blockade from tubocurarine in an isolated arm. When tubocurarine concentrations were reduced by deflating the arterial tourniquet the systemic deflating the arterial tourniquet the systemic administration of neostigmine increased the recovery rate. Systemic administration of neostigmine 5 min before isolation of an arm and injection of tubocurarine shortened the duration of neuromuscular blockade. The authors concluded that, unless a relaxant concentration gradient exists from receptor to blood, antagonism of neuromuscular blockade would be impossible even with large doses of neostigmine (Feldman and Agoston, 1980).

An opposing argument can be formulated from the results of several other studies. The magnitude of neuromuscular blockade achieved during studies utilizing a continuous systemic infusion of tubocurarine is approximately equal to that obtained in the isolated arm experiments (Miller et al., 1974; Cronnelly, Morris and Miller, 1982). Since the neuromuscular block remained stable as long as the infusion continued or the tourniquet remained inflated, concentration gradients between blood and receptor were minimal or non-existent in either case. Neostigmine, pyridostigmine and edrophonium produce antagonism during continuous tubocurarine infusion, yet neostigmine was unable to do so under similar gradient conditions in the isolated arm. Differences in the time required for onset of action may explain this discrepancy. Deflation of the tourniquet before the onset of a neostigmine effect would result in a "wash-out" of both drugs without alteration of the already maximal tubocurarine effect. When neostigmine is administered first, there is evidence of its action in that the duration of the tubocurarine block is shortened. Both magnitude and duration of blockade were decreased when neostigmine preceded tubocurarine by as much as 180 min (Blitt, Moon and Kartchner, 1976). This antagonism would occur at a time when neostigmine was being "washed out" and a concentration gradient for relaxant was present from blood toward receptor, that is "washed in".

Based on these data, antagonism does occur in the presence of relaxant concentration gradient from blood to receptor and also in the absence of gradients when blood and receptor are in dynamic equilibrium. Although a gradient away from the receptor may increase the rate of spontaneous recovery (Agoston, Feldman and Miller, 1979) and therefore may facilitate antagonism, the presence of such a gradient does not appear to be the prime controlling factor. The concentration of non-depolarizing muscle relaxant at the receptors and the dissociation constants themselves, may be of greater import.

TESTS OF NEUROMUSCULAR FUNCTION

The fraction of receptors required for neuromuscular function in animals has been established by determining dose–response curves for suxamethonium depolarization in the presence and absence of tubocurarine (receptor occlusion technique) and autoradiographic determination of receptors irreversibly bound by alpha-bungarotoxin (Paton and Waud, 1967; Chang, 1978). The fact that muscle twitch tension is not reduced until more than about 70% of the receptors are blocked demonstrates the large margin of safety that exists during neuromuscular transmission.

The receptor occlusion technique has also been used to estimate the fraction of receptors occupied by relaxant at times when tests dependent on nerve stimulation have returned to control (Waud and Waud, 1971, 1972). These data also been correlated with other clinical tests of neuromuscular function (Miller, 1976), and head lift, hand grip and inspiratory force appear to be more stressful to the neuromuscular junction and require a higher percentage of receptors free of muscle relaxant to allow a normal response. Because they require more receptors, the more stressful tests would be most sensitive in detection of residual muscle relaxant effect or inadequate antagonism of that block. In view of other evidence the order of sensitivity and equivalence of a particular clinical test to another using nerve stimulation may require revision.

More recent studies have suggested that head-lift and train-of-four (TOF) are of equal sensitivity and that TOF may be more sensitive than a sustained response to 5 s of tetanic stimulation at 50 Hz (Brand et al., 1977; Ali et al., 1981). Also, electromyograph recordings of discharge frequencies in human limb muscles during voluntary contractions found ranges of 5–30 Hz and did not exceed 40–60 Hz. Measurements of maximal strength of voluntary thumb adduction were found not to exceed that produced by tetanic stimulation at 50 Hz (Merton, 1954; Person and Kudina, 1972; Milner-Brown, Stein and Yermm, 1973; Epstein and Epstein, 1973). These data suggest that voluntary efforts such as hand-grip or head-lift may occur within a frequency range which does not exceed 40–60 Hz, and are therefore not equal to tetanic stimulation at 100 and 200 Hz for 5 s, as previously suggested.

Muscular efforts measured by the clinical tests (for example vital capacity, inspiratory and expiratory force, head-lift, hand-grip,) are produced in response to a range of physiological frequencies, requiring a similar fraction of the receptor population for normal responses. Some tests may be more sensitive than others, however; the increase in the fraction of receptors with increasing sensitivity of the test is small and the approximate number of receptors required by all the clinical tests would be similar. More important, the majority of receptors can still be occupied by relaxant at the time the clinical tests are normal. Although normal TOF, 50-Hz tetanus and head-lift predict that responses to physiological frequencies are unimpaired, they do not estimate the fraction of receptors in excess of those required for normal transmission, that is the margin of safety. Without a margin of safety, any decrease in the number of free receptors, for example through drug interactions, would compromise the neuromuscular response to stimulation at physiological frequencies, leaving the patient at risk.

The response to high frequency (100, 200 Hz) tetanus in animals may fade as a result of presynaptic rather than postsynaptic relaxant effect. However, a sustained response occurred when 50–77% of receptors are free of tubocurarine (Waud and Waud, 1971; Bowman and Webb, 1976). Sustained response at these frequencies may be useful clinically to estimate a higher fraction of free receptors than other tests. In anaesthetized man, however, tetanic fade at high frequencies can occur in the absence of relaxant, an effect which is dependent on the duration of stimulation. Perhaps this results from the effects of anaesthetic agents in neuromuscular transmission. After 1 s of tetanic stimulation at 200 Hz, the tetanic fade ratio demonstrated no 0.9 fade (i.e. ratio of 1.0), but after 3 s the ratio was 0.8, after 5 s 0.7 and after 10 s 0.55 (Stanec et al., 1978). The response to 100 Hz was sustained at a stimulation period of 3 s (Heisterkamp, Skovsted and Cohen, 1969). Tetanic stimulation for 0.5 s produced a sustained response to frequencies from 50 to 200 Hz in the absence of relaxant. During partial neuromuscular blockade the response to tetanic stimuli was not sustained at higher frequencies even when the response to lower frequency stimulation and muscle twitch had returned to control (Gissen and Katz, 1969). Sustained response to high-frequency tetanic stimulus can be obtained and may provide clinically useful information by estimating the return of a margin of safety to neuromuscular transmission.

NON-PHARMACOKINETIC CONSIDERATIONS WHEN ANTAGONISM IS INADEQUATE

Intensity of block. The speed of antagonism can be influenced by the magnitude of neuromuscular blockade, the antagonist and its dose. Antagonism of neuromuscular blockade (>80% block) with neostigmine 2.5 mg may require 8–27 min for complete recovery of muscle twitch height or even longer for sustained contraction in response to tetanic stimulation at 50 or 100 Hz (Katz, 1971), whereas less than 80% neuromuscular blockade required 3–14 min. If edrophonium is chosen as the antagonist, the onset of action (i.e. time to peak antagonism) is more rapid than from neostigmine, pyridostigmine or 4-aminopyridine (Miller et al., 1974; Ferguson, Egerszegi and Bevan, 1980).

Acid–base and electrolytes. Non-depolarizing neuromuscular blockade is potentiated by significant respiratory acidosis ($Pa_{CO_2} > 50$ mm Hg) while complete antagonism is prevented. This problem does not occur with metabolic acidosis, but antagonism is prevented by metabolic alkalosis (Miller, Van Nyhuis and Eger, 1975; Miller, 1976; Miller and Roderick, 1978). From a clinical standpoint, postoperative respiratory depression from residual anaesthesia and narcotic analgesics may augment a neuromuscular blockade and prevent its antagonism. Correction of the respiratory acidosis by ventilation should precede the administration of more anticholinesterase agent.

The clinical importance of metabolic alkalosis remains unclear. Although a significant effect was present in animals, the pH was acutely increased with bicarbonate and probably does not reflect the clinical situation. During surgery, patients with metabolic alkalosis probably have been alkalotic for several hours or days and may also have associated electrolyte changes. In view of the lack of information, it would be preferable to restore acid–base status to normal in alkalotic patients.

Alterations of potassium, calcium and magnesium may also accompany these acid–base changes. Non-depolarizing neuromuscular blockade may be augmented by hypermagnesaemia, hypokalaemia or hypocalcaemia (del Castillo and Engbaek, 1954; Feldman, 1963; Cohen, 1966; Monthey, 1966; Ghoneim and Long, 1970; Cunningham, Carter and Rector, 1971; Feldman, 1973). After 15 days of administration of diuretic to animals without potassium supplementation, less pancuronium was required to produce neuromuscular blockade and more neostigmine was required for antagonism. The potassium effect was small and complete antagonism of the neuromuscular block could be achieved by increasing the dose of neostigmine (Miller and Roderick, 1978). If the results of these studies reflect the clinical situation, then changes in potassium appear to be of minor consequence.

Drug interactions. Inadequate antagonism may also be attributed to interactions with other drugs used during anaesthesia and surgery. Probably of greatest clinical significance is the neuromuscular blockade produced by antibiotics, which usually resembles that produced by tubocurarine in its response to peripheral nerve stimulation (fade of muscle contraction in response to tetanic stimulation and post-tetanic facilitation). Therefore, how much of the residual blockade is caused by the antibiotic and how much is caused by the muscle relaxant usually cannot be determined. Unfortunately, neostigmine (up to 5 mg/70 kg) may provide inconsistent or partial reversal and in some cases (such as with Polymyxin B) it may augment the block. Calcium (up to 1 g/70 kg) often produces incomplete and transient antagonism of neuromuscular blockade and may antagonize the antibacterial action of the antibiotics (Fisk, 1961; Stanley, Giesecke and Jenkins, 1969; Pittinger and Adamson, 1972; Dretchen, Sokoll and Gergis, 1973; Adams and Mathew, 1974; Fogdall and Miller, 1974a, b; Van Nyhuis, Miller and Fogdall, 1976). If antagonism fails, mechanical ventilation is indicated until the block spontaneously remits.

CARDIOVASCULAR EFFECTS OF THE ANTAGONISTS

The use of anticholinesterase drugs as antagonists of non-depolarizing neuromuscular blockade has been accompanied by cardiovascular complications. Arrhythmias and cardiac arrest have been reported following the administration of neostigmine and atropine (Bain and Broadbent, 1949; Clutton-Brock, 1949; Hill, 1949; MacIntosh, 1949; Lawson, 1956; Pooler, 1957). As a result, various techniques have been described to enhance the safety of reversal. These include: hyperventilation to produce respiratory alkalosis, simultaneous injection of atropine and neostigmine, slow administration of neostigmine and atropine in a ratio of 2.5 : 1 and maintenance of adequate oxygenation throughout the period of reversal (Pooler, 1957; Riding and Robinson, 1961; Kemp and Morton, 1962; Wylie and Churchill-Davidson, 1972; Baraka, 1968). The most useful information gained from these studies was the determination of the correct atropine dose to be mixed with neostigmine.

The cardiac arrests have been attributed to cholinergic (muscarinic) stimulation of the heart by neostigmine combined with insufficient atropine. The simultaneous administration of atropine causes a brief (< 10 min) but significant tachycardia which occurs as a result of a slower onset of action of neostigmine. The relationship of arrhythmias such as inverted P waves, Wenckeback phenomena, premature atrial contractions, junctional rhythms, A–V dissociation, premature ventricular contractions and bigeminy to atropine, neostigmine or their combination is less clear (Gottlieb and Sweet, 1963; Baraka, 1968; Ovassapian, 1969; Salem et al., 1970; Tan, Balasaraswathi and El-Etr, 1980). Many studies were performed during emergence from anaesthesia, when changing anaesthetic concentrations, surgical stimulation and ventilation may have caused the arrhythmias. However, arrhythmias occur even when those variables are held constant (Fogdall and Miller, 1973; Cronnelly, Morris and Miller, 1982). Decreasing the amount of atropine or replacing it with another anticholinergic such as glycopyrrolate has been suggested to attenuate the tachycardia and the frequency of other arrhythmias (Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Fogdall and Miller, 1973; Gyermek, 1975, 1977). In view of this, the antagonist that requires the least amount of atropine to prevent bradycardia may provide an advantage clinically in terms of less arrhythmia. Both edrophonium and pyridostigmine have been suggested to have less muscarinic effects than neostigmine, while 4-aminopyridine has no muscarinic stimulant property (Randall, 1950; Osserman, 1955). When 4-aminopyridine is combined with neostigmine or pyridostigmine, approximately 5 $\mu g\,kg^{-1}$ of atropine is required to prevent bradycardia (Miller, Booij and Agoston, 1979). The atropine dose must be increased to 15 $\mu g\,kg^{-1}$ when either neostigmine or pyridostigmine are used alone (Fogdall and Miller, 1973). Edrophonium 0.5 $mg\,kg^{-1}$ required less atropine (7 $\mu g\,kg^{-1}$) to prevent bradycardia. Reduction of the dose of atropine resulted in less tachycardia; however, transient junctional rhythms were still prominent, but without significant changes in mean arterial pressure (Cronnelly, Morris and Miller, 1982).

Glycopyrrolate reduces the tachycardia response and markedly decreases the frequency of arrhythmias when combined with neostigmine, pyridostigmine or edrophonium (Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Gyermek, 1977). Although a greater frequency of arrhythmia occurs with atropine, there is insufficient evidence to implicate it as the aetiological agent. Perhaps glycopyrrolate blocks the arrhythmogenic stimulus of the anticholinesterase agents more effectively than atropine.

The use of antagonists without muscarinic activity or muscle relaxants that do not require reversal may be needed to abolish the problem of arrhythmia.

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SUXAMETHONIUM

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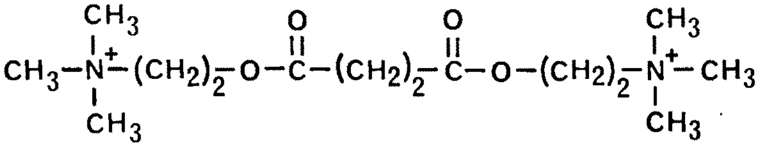
Suxamethonium (succinyldicholine) was first described in 1906 by Hunt and Taveau amongst a series of choline analogues which were tested in curarized cats. As is well known, the use of curarized cats by Hunt and Taveau (1906) obscured the neuromuscular blocking property of suxamethonium which went unrealized for another 40 years or so until described by Bovet and colleagues (1949) and Phillips (1949). Although initially thought to be too transient in its neuromuscular blocking effect to be useful clinically, the potential of suxamethonium was soon recognized and the drug was introduced to clinical practice in Europe by Brücke and colleagues (1951) and in the U.S.A. by Foldes, McNall and Borrego-Hinjosa (1952). Since that time, suxamethonium has enjoyed widespread use as the only short-acting muscle relaxant available, and consequently its rather undesirable side-effects have been tolerated (see Side-effects and Complications). However, in recent years the possibility of a non-depolarizing muscle relaxant of short duration has become more of a reality and it is likely that suxamethonium will become mainly of historical interest. This review may well be a requiem for suxamethonium.

Chemically, suxamethonium is two acetylcholine molecules joined back-to-back (fig. 1) and, whilst suxamethonium possesses a depolarizing action in common with acetylcholine, its duration of effect is somewhat longer because of its slower hydrolysis by pseudocholinesterase (plasma cholinesterase) (EC 3.1.1.8). This action of suxamethonium is fairly straightforward when compared with the effects manifested clinically, which are often confusing. This review is an attempt to present to the reader the current status of suxamethonium and what to bear in mind when using this particular muscle relaxant.



$$CH_3-\overset{CH_3}{\underset{CH_3}{N^+}}-(CH_2)_2-O-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-O-(CH_2)_2-\overset{CH_3}{\underset{CH_3}{N^+}}-CH_3$$

FIG. 1. The chemical structure of suxamethonium.

THE NATURE OF SUXAMETHONIUM BLOCK

Suxamethonium depolarizes skeletal muscle fibres from their normal resting membrane potential of about −90 mV towards a more positive potential above the threshold at which the end-plate potential can trigger a muscle action potential, thus neuromuscular transmission is effectively blocked by depolarization. This mechanism of action was advanced by Burns and Paton (1951) to explain the action of another depolarizing agent, decamethonium, at about the same time suxamethonium was introduced into clinical practice. There was no doubt that suxamethonium, like decamethonium, did depolarize the end-plate, but it soon became apparent that the type of block produced by these agents was more complex than first believed. Zaimis (1953) and Jenden, Kamijo and Taylor (1954) described some characteristics of depolarizing block which were more akin to non-depolarizing block. It is now well established, but not completely understood, that the block produced by suxamethonium is not entirely paralleled by its depolarizing effect, with the emergence of some of the characteristics of non-depolarizing block. Based on his observations on isolated skeletal muscle preparations, Jenden (1955) introduced the terms "phase I" and "phase II" block to describe the two types of effect seen

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with depolarizing agents. These terms, now applied to the clinical situation with suxamethonium, are familiar to most anaesthetists. "Phase II" block has also been described as "dual" block or "desensitization" block (Churchill-Davidson, Christie and Wise, 1960).

Clinical studies of "phase II" block produced by suxamethonium have been hampered by the fact that this "phase" is not always observed, is sometimes slow to develop and does not always assume all the characteristics of non-depolarizing block. Consequently, despite the fact that suxamethonium has been used in clinical practice for 30 years, the phenomenon of "phase II" block is still neither clearly defined nor understood.

"Phase I" block

Upon i.v. administration of the initial dose of suxamethonium, depolarization of skeletal muscle fibres is often accompanied by transient fasciculations during the onset of "phase I", and sometimes by a slight increase in the tension of indirectly elicited twitch responses. The fasciculations are followed by a rapid onset of neuromuscular block. At this point the neuromuscular block is classed as "phase I" and exhibits the following characteristics during partial paralysis:

(i) Well-sustained tetanus. During stimulation at 50–100 Hz the mechanical response is well sustained and muscle action potential height is maintained;

(ii) no post-tetanic facilitation of twitch height (twitches elicited indirectly at 0.1 Hz are not increased in tension if preceded by a tetanic stimulus of 50 Hz for 5s);

(iii) a train-of-four (TOF) ratio (T_4/T_1) of greater than 0.7 (the amplitude of the last twitch of a train-of-four at 2 Hz is greater than 0.7 of the first, $T_4/T_1 > 0.7$);

(iv) potentiation of block by an anticholinesterase.

These characteristics have been described by many workers (Churchill-Davidson, Christie and Wise, 1960; Katz, Wolf and Papper, 1963; Ali and Savarese, 1976), and are generally accepted. The use of tetanic maintenance as a test has declined because of its unreliability and is now not regarded as definitive (Crul et al., 1966).

"Phase II" block

"Phase II" is usually preceded by "phase I" block and is characterized by the following:

(i) A poorly sustained tetanus. A decrease in mechanical tension during continued stimulation (fade) and a decrease of action potential amplitude despite the continued stimulation;

(ii) post-tetanic facilitation;

(iii) a T_4/T_1 ratio of less than 0.3;

(iv) reversal of block by anticholinesterase agents;

(v) repetitive doses result in progessively less neuromuscular block (tachyphylaxis). This may occur in some, but not necessarily all, patients.

There is no doubt that the mode of action of suxamethonium changes with time, but considerable controversy exists as to the characteristics, time-course and mechanism of "phase II" block. Contributing to this confusion and controversy are several factors. First, the characteristics listed above do not all appear simultaneously, but rather during a gradual transition; Churchill-Davidson, Christie and Wise (1960) list five stages of development of "phase II" block, the last of which is emergence of all the signs of non-depolarizing neuromuscular block. Second, the onset of "phase II" block is time- and dose-dependent (Crul et al., 1966). Third, too much emphasis is placed on the characteristics listed above as being absolute indices of "phase II" block (Waud and Waud, 1975). Finally, the route of administration (Walts and Dillon, 1967), the anaesthetic used (DeCook and Goudsouzian, 1980), the muscle studied, patient variation and whether repeated doses or a continuous infusion is used (Katz, 1973), all will contribute to marked variation. The anaesthetist should be aware of the unpredictable manner in which the action of suxamethonium can change with time, and, if possible, use a non-depolarizing agent if neuromuscular block of a longer duration is desired.

What are the underlying mechanisms for the change of the mode of action of suxamethonium? It is clear that the neuromuscular block produced by suxamethonium is not totally a result of depolarization, since in isolated muscle preparations the depolarization produced by suxamethonium is transient whilst the neuromuscular block persists (Gissen and Nastuk, 1970). In our own laboratory, using isolated amphibian muscle, we have observed the decline of the end-plate response to nerve stimulation over 30 min during continual exposure to suxamethonium despite the membrane potential being held at a constant −90 mV (resting amphibian muscle membrane potential ≈ −90 mV) (personal observation). Katz and Thesleff (1957) demonstrated that suxamethonium, like acetylcholine, produced ***desensitization*** of the neuromuscular junction of amphibian muscle *in vitro*, an observation confirmed by other workers (Gissen and Nastuk, 1970). Densensitization is regarded as the process which the acetylcholine receptor undergoes in the continued presence of an agonist from an "effective" to "inactive" state (Katz and Thesleff, 1957). Whether desensitization observed *in vitro* corresponds to the "phase II" block observed in patients is a matter of conjecture.

Some workers have also postulated that "phase II" block may be the result of a prejuctional action of the drug (Standaert and Adams, 1965; Galindo, 1971).

Use of train-of-four for differential diagnosis

The onset of "phase II", as described above, may not be clear and the different characteristics probably will not appear simultaneously. In spite of these limitations, the use of train-of-four as a diagnostic aid (fig. 2) for the change of the mode of action of suxamethonium has gained popularity and acceptance in recent years. The advantage of this test is that it can be applied fairly frequently, about once every 12 s, without influencing the block (Lee, 1975). Savarese and others (1975) have shown train-of-four to be a useful and valid clinical test of "phase II" block. The T_4/T_1 ratio value of 0.3 or less when the suxamethonium block changes was also recently confirmed during long-term suxamethonium block (Ramsey et al., 1980). Of the limited number of tests available to monitor the transition of the action of suxamethonium, the train-of-four test is probably one of the more clinically practical and useful, as long as it is not regarded as a definitive test. Also of value is the appearance of post-tetanic facilitation during the change of the mode of action of suxamethonium. A post-tetanic twitch which is at least three times as large as the pre-tetanic twitch would be considered indicative of a change of action (fig. 3).

DOSE–RESPONSE RELATIONSHIPS

The short duration of action of suxamethonium and the fact that a block of 90–100% is utilized clinically makes the dose–response relationship of only academic value. It is of more clinical use to

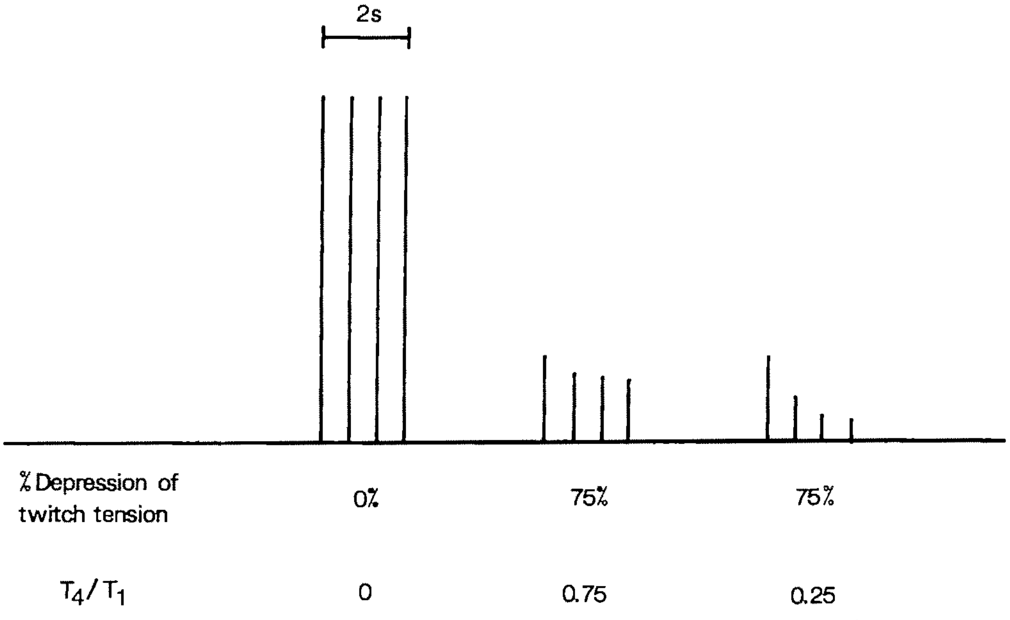

FIG. 2. Diagrammatic illustration of the use of the train-of-four test to diagnose the change of the mode of action of suxamethonium as shown by the change of the T_4/T_1 ratio from 0.75 to 0.25. A ratio of 0.75 is indicative of depolarizing neuromuscular block and a ratio of 0.25 indicates that the block produced by suxamethonium is no longer a result of pure depolarization.

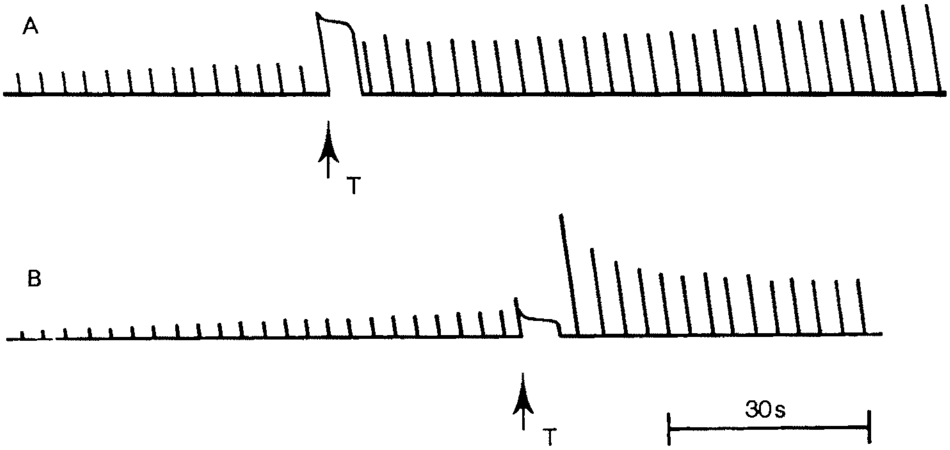

FIG. 3. Diagrammatic illustration of the use of post-tetanic facilitation to indicate the change of the mode of action of suxamethonium. In A there is little post-tetanic facilitation indicating that suxamethonium is exhibiting the characteristics of mainly depolarizing neuromuscular block; while in B there is marked post-tetanic facilitation indicating that the neuromuscular block produced by suxamethonium is not a result of pure depolarization.

appreciate the dose–time course relationship. Katz and Ryan (1969) studied the relationship of doses of suxamethonium 0.5–5 mg kg^{-1} on the time-course of effect in patients. These results are regraphed in figure 4. In all patients, the indirectly elicited twitch was totally abolished. Two points are illustrated by this study. First, there is wide variation of patient response to doses

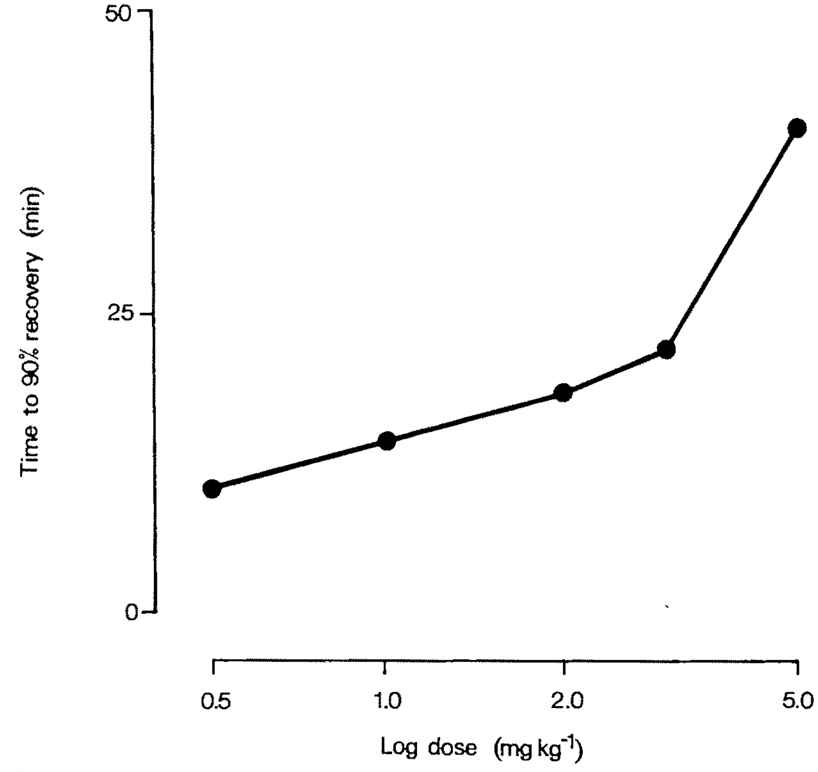

FIG. 4. The relationship between the log dose of suxamethonium and the time to 90% recovery from neuromuscular blockade. Original patient data from Katz and Ryan (1969).

of suxamethonium used clinically. Second, the recovery time from suxamethonium is slower than generally appreciated; for example, a dose of 1 mg kg^{-1} may produce a time from the first depression of twitch tension to 90% recovery as long as 21 min.

Single bolus dose

The rapid onset of action of suxamethonium has, in the past, been the main justification for using a single bolus dose (often used in the so-called "rapid sequence" or "crash-induction") and will probably remain the justification, by those who use it, for its continued use. It is in this context that suxamethonium is of the most advantage. A single bolus dose of less than 2 mg kg^{-1} is unlikely to produce signs of "phase II" block, although a multitude of side-effects may manifest themselves, including marked fasciculations, muscle pain after operation, increased intragastric pressure and cardiac arrhythmias. The use of repeated single-dose administrations is not often indicated. If repeated sufficiently, tachyphylaxis and even "phase II-block" can occur, and may even be part of the same phenomenon (Sugai, Hughes and Payne, 1975).

Continuous infusion

The continuous infusion of suxamethonium for more than 1 h is regarded by some as the misuse of a short-acting muscle relaxant when there is a large range of non-depolarizing agents available, the effects of which are reversible and predictable, unlike the effects of a prolonged (greater than 1 h) infusion of suxamethonium (Katz and Katz, 1975). In our opinion, the main value of continuous infusion of suxamethonium is for procedures such as endoscopic examinations, when relatively short periods of relaxation are required. It should be pointed out that there is a large number of clinicians—particularly in the United States—who still use the continuous infusion of suxamethonium for all kinds of cases. We believe that this practice will markedly decrease during the next 10 to 20 years.

As with single doses, the patient variation in response to continuous infusion of suxamethonium is wide. An infusion rate of between 2 and 15 mg kg^{-1} h^{-1} has been reported as that required for maintenance of approximately 90% twitch depression (Katz and Ryan, 1969; Ramsey et al., 1980). Despite the onset of "phase II" block in the study of Katz and Ryan (1969), the rate of infusion did not need to be changed and in the study of Ramsey and colleagues (1980), only eight of 32 patients required alteration of the infusion rate. Thus, the appearance of "phase II" block during continual infusion is well established, but when this occurs is unpredictable (Crul et al., 1966; Katz and Ryan, 1969). It is this latter factor which also makes the recovery rate unpredictable, since recovery from "phase II" block may be slower than from "phase I" block. This point is still the subject of debate and the results depend a great deal upon the circumstances. Monitoring the train-of-four ratio will help to some extent, a T_4/T_1 ratio of less than 0.3 indicating that a prolonged recovery time might occur in some patients.

Adults and children

Since infants have a proportionally smaller muscle mass and lower pseudocholinesterase concentrations than adults (Zsigmond and Downs, 1971), it might be expected that infants would be more susceptible to suxamethonium than adults. This is not necessarily so (Telford and Keats, 1957). Several groups of workers have investigated infant resistance to suxamethonium; Nightingale, Glass and Bachman (1966) found that, although the depth of block with suxamethonium could not be demonstrated to be related to age, the recovery time in infants was faster, a finding confirmed by Cook and Fischer (1975). Walts and Dillon (1969a) concluded that infant resistance to suxamethonium is artefactual, since the discrepancy between adults and infants is removed if the dose is calculated in terms of body surface area rather than body weight. This finding was also confirmed by Cook and Fischer (1975). The reason for body surface area giving a more accurate estimation of the dose of suxamethonium may lie in the fact that blood volume and extracellular fluid volume correlate more constantly with body surface area throughout life than with body weight, an important factor in the pharmacokinetics of suxamethonium.

Twitch v. *electromyogram*

In recent years the use of the neurally-evoked compound electromyogram (e.m.g.) recording has been described as a clinical method of monitoring neuromuscular transmission (Epstein and

Epstein, 1975; Lee et al., 1977). This method of monitoring has two advantages over the twitch recording technique using a force-displacement transducer. First, it is easier to set up than the twitch recording technique since only two recording electrodes on the muscle are needed, rather than a force-displacement transducer attached indirectly to the muscle. Second, patient movement does not interfere with the recording. The main disadvantage of this technique is recording the signal; the e.m.g., which is composed of the compound muscle action potential, is a fast event beyond the frequency-response range of most pen recorders, and therefore either an oscilloscope or an alternative method of recording is needed in order to interpret the signal. Epstein and Epstein (1975) and Lee and colleagues (1977) describe a method of digital time-base expansion which enables the e.m.g. signal to be recorded on a pen recorder, thus overcoming most of the technical difficulties associated with recording of the e.m.g. response.

Simultaneous recording of the twitch and e.m.g. responses during suxamethonium neuromuscular block has revealed more information about the action of the drug. The neuromuscular refractory period has been shown to be prolonged in patients by giving subparalytic doses of suxamethonium (Epstein and Jackson, 1973), and also Katz (1973) demonstrated clinically that "phase I" and "phase II" block could be clearly distinguished by using simultaneous recording. Katz (1973) also found that the depth of block estimated from the depression of twitch tension differs from the depth of block estimated from the depression of the e.m.g. when recorded from the adductor pollicis muscle. Thus, use of the e.m.g. recording can be easier than twitch recording, can give more information than the twitch recording, and can, if used in combination with the twitch recording, give considerably more information than either alone.

CLINICAL INDICATIONS FOR USE OF SUXAMETHONIUM

The primary clinical indication for the use of suxamethonium is for a rapid onset and short duration of neuromuscular block. It is particularly suited for rapid induction techniques. Once tracheal intubation has been achieved, a non-depolarizing neuromuscular blocking agent is often satisfactorily used for the maintenance of muscle relaxation throughout the rest of anaesthesia. As described earlier in this review, there is little indication for the use of a continuous infusion of suxamethonium.

Outside the operating room, suxamethonium has been used with success for the control of muscle activity during electroconvulsive therapy (Karis, 1975). Suxamethonium is particularly suitable for this purpose because of its short duration, and because it virtually eliminates the possibility of bone fractures. Some patient risk is associated with the use of suxamethonium during ECT because of the side-effects of this drug, particularly cardiac arrest (Karis, 1975) (see Side-effects and Complications.)

MODIFICATION OF ACTION

Suxamethonium owes its short duration of action to its rapid enzymic destruction by pseudocholinesterase (fig. 5). If the blood concentration of pseudocholinesterase is low or if the activity of the enzyme is decreased, then the duration of action of suxamethonium will be prolonged. Factors which can affect pseudocholinesterase are discussed below.

Atypical pseudocholinesterase concentrations

In most populations, the normal genotype for pseudocholinesterase is $E_1^u E_1^u$ and has a

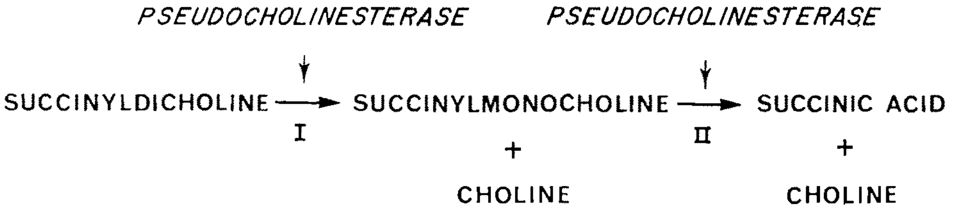

FIG. 5. The enzymic fate of suxamethonium (succinyldicholine); step I is approximately six to seven times faster than step II.

frequency of 96%; at the other end of the scale is the genotype $E_1^sE_1^s$ with a frequency of 1 in 100 000, and in such cases pseudocholinesterase is absent or too low to measure (Whittaker, 1980). Between the two ends of the scale are a range of genotypes who are moderately or very sensitive to suxamethonium, the overall frequency of this group being about 1 in 2500 (Viby-Mogensen and Hanel, 1977b). Patients with atypical pseudocholinesterase concentrations will exhibit prolonged neuromuscular block to suxamethonium, usually characterized by apnoea (Viby-Mogensen and Hanel, 1977a). Units in Britain (Whittaker, 1980) and Denmark (Viby-Mogensen and Hanel, 1977b) have been established to screen suspected cases of atypical pseudocholinesterase concentrations and their relatives in order to alert physicians to their increased sensitivity. Whittaker (1980) reports that the issue of cards to patients warning of increased sensitivity has taken on a new role as one physician wrote to inquire about membership in "The Cholinesterase Club". Units such as the ones in Britain and Denmark obviously take a step in the right direction towards decreasing the probability of prolonged neuromuscular block in patients with atypical pseudocholinesterase concentrations. If such cases are encountered, the only course open to the anaesthetist is prolonged ventilation and the possible treatment with purified human pseudocholinesterase (Goedde, Atland and Schloot, 1968). Artificial ventilation is recommended. If a peripheral nerve stimulator is used to monitor the patient, diagnosis of prolonged neuromuscular block with suxamethonium should be made after the first dose, and thus only a few hours of ventilation will be required.

Decreased pseudocholinesterase concentrations during pregnancy

A decrease of 25–30% of blood pseudocholinesterase concentrations during late pregnancy and the early post-partum period is well known (Hazel and Monier, 1971). Since the role of pseudocholinesterase in the blood is not known, the reason behind the decrease of the enzyme concentration during pregnancy cannot be explained. There is no correlation between pseudocholinesterase concentrations during pregnancy and the duration of action of suxamethonium (Blitt et al., 1977), and therefore it would be inappropriate to contraindicate the use of suxamethonium during pregnancy other than to warn of the occasional cases of prolonged apnoea and the complications normally associated with this muscle relaxant. The use of magnesium sulphate for toxaemia of pregnancy, whilst not affecting pseudocholinesterase, will render neuromuscular transmission more sensitive to suxamethonium and an increased duration of action of suxamethonium may be observed (Morris and Giesecke, 1968).

For further information on atypical pseudocholinesterase concentrations, the reader is referred to a recent review by Whittaker (1980).

Acquired causes of decreased pseudocholinesterase concentrations

Whittaker (1980) lists 13 acquired causes of decreased pseudocholinesterase concentrations and it is possible that the anaesthetist may encounter any one on the list. The most likely are liver diseases (acute hepatitis and hepatic metastasis) since pseudocholinesterase is synthesized in the liver; muscular dystrophy; carcinomas; surgical shock; hyperthyroidism; tetanus and typhus. Burn patients also have a reduced pseudocholinesterase concentration as well as being at risk of hyperkalaemia produced by suxamethonium. Also recently reported was a case of reduced pseudocholinesterase concentrations following plasmaphoresis (Evans, MacDonald and Robinson, 1980).

Drugs which affect pseudocholinesterase activity

Anticholinesterase agents do, as would be expected, markedly affect the time-course of action of suxamethonium; however, the type of effect will depend on whether "phase I" or "phase II" block is predominant. Katz, Wolf and Papper (1963) reported that during "phase I" block, the action of suxamethonium was increased by edrophonium, whilst during "phase II" block the action of suxamethonium was antagonized. These workers found the presence of post-tetanic facilitation was the best guide in predicting the response to edrophonium. Lee (1976) reported that edrophonium antagonizes clinical suxamethonium block provided that the T_4/T_1 ratio was less than 0.5. The use of the long-acting anticholinesterase ecothiopate iodide (phospholene) in eyedrops has been shown to prolong the action of suxamethonium (Katz and Katz, 1966).

Tacrine and hexafluorenium are two agents which have been used to prevent the enzymic destruction of suxamethonium as a method of prolonging its duration of effect (Foldes et al., 1960; Karis, Nastuk and Katz, 1966). Clinically, hexafluorenium is usually injected before suxamethonium, since the two given together can result in bronchospasm. Hexafluorenium also possesses a weak neuromuscular blocking action which can help prevent the fasciculations which can occur with the initial administration of suxamethonium. This technique of prolongation is not widely used, perhaps as a result of the undetermined nature of the block (Walts, DeAngelis and Dillon, 1970), but mainly because this combination has no advantages over a non-depolarizing neuromuscular blocking agent. There are, however, pockets of enthusiasm for this combination in both the United States and United Kingdom.

Many other agents are known to affect the duration of action of suxamethonium by interfering with pseudocholinesterase. Procaine competes with suxamethonium for pseudocholinesterase (Foldes et al., 1953). Pancuronium is a potent inhibitor of pseudocholinesterase (Stovner, Oftedal and Holmboe, 1975), although at clinically used doses the inhibition by pancuronium is not a major influence on the action of suxamethonium (Schuh, 1977). Oral contraceptives decrease pseudocholinesterase activity by about 20% (Robertson, 1967); the monoamine oxidase inhibitor phenelzine can produce complications (Bodley, Halwax and Potts, 1969); the anti-cancer agents AB-132 and cyclophosphamide also decrease pseudocholinesterase activity (Wang and Ross, 1963; Walker, Zapf and Mackay, 1972) as do x-ray therapy (Hodges and Harkness, 1972) and organo-phosphorus insecticides (Barnes and Davies, 1951). Chlorpromazine has been shown to depress pseudocholinesterase *in vitro* (Erdös et al., 1956).

Modification of action by other drugs

Included in this class are drugs which interact with suxamethonium at the neuromuscular junction rather than indirectly via inhibition of pseudocholinesterase, as described above. The most commonly encountered drug interaction with suxamethonium is probably with a non-depolarizing neuromuscular blocking agent as these two agents are often used together. A small dose of a non-depolarizing agent is often administered before suxamethonium in order to reduce fasciculations (see Side-effects and Complications). Pancuronium given in this way does not significantly increase the effect of suxamethonium (Katz, 1971), although under similar conditions tubocurarine does slightly diminish the intensity and duration of action of suxamethonium (Walts and Dillon, 1969b; Miller and Way, 1971). The opposite interaction has been reported between suxamethonium and gallamine (Brennan, 1956) although this was not confirmed by Miller and Way (1971). The reverse situation (suxamethonium given before a non-depolarizing agent) also results in an interaction. The intensity and duration of action of pancuronium was increased by prior administration of suxamethonium (Katz, 1971). While the interaction between non-depolarizing muscle relaxants and suxamethonium is reasonably straightforward as described above, the situation is much more complicated if tubocurarine is given during an established neuromuscular block with suxamethonium or *vice versa*. Under these circumstances, depending on the dose given and the nature of the suxamethonium block, either antagonism of effect or an increase of magnitude of effect may occur. Because of the uncertainty of the response, it appears best to avoid such pharmacological roulette.

Other drugs which are known to potentiate the action of suxamethonium on neuromuscular transmission include magnesium sulphate (Morris and Giesecke, 1968), lithium carbonate (Hill, Wong and Hodges, 1976) and propanidid (Doenicke et al., 1968).

SIDE-EFFECTS AND COMPLICATIONS

The side-effects which may be encountered with suxamethonium are as follows:

(i) Muscle fasciculations;
(ii) postoperative muscle pain;
(iii) hyperkalaemia (increased potassium blood concentrations);
(iv) increased intraocular pressure;
(v) increased intragastric pressure;
(vi) cardiovascular effects.

The complications which may be encountered with suxamethonium include atypical pseudocholinesterase concentrations (already described), malignant hyperthermia, myotonia and myoglobinuria.

Side-effects

(i) Muscle fasciculations. This transient phenomenon is often observed during the onset of "phase I" neuromuscular block with suxamethonium and is coincidental with the initial depolarization of muscle fibres. Churchill-Davidson (1954) found a correlation between suxamethonium-induced fasciculations and pain after operation; this effect was studied further by Collier (1975), who found a relationship between high frequency discharge rates in the e.m.g. recordings made from fasciculating muscle and pain after operation. This correlation is probably complicated by the fact that some postoperative pain is inevitable whether suxamethonium is used or not (Brodsky and Ehrenwerth, 1980). A direct relationship has been established between the degree of muscle fasciculation and the observed increase in intragastric pressure (Miller and Way, 1971), and various ways of diminishing muscle fasciculations have been studied. Pretreatment with a low dose of suxamethonium ($0.2\,mg\,kg^{-1}$) before administering a larger dose before intubation was found by Baraka (1977) to decrease the frequency of muscle fasciculation. Baraka (1977) used the term "self-taming" to describe this technique. However, his technique still produces an increase in intraocular pressure with the "self-taming" dose (Meyers, Singer and Otto, 1980). Other pretreatments include a small dose of one of the non-depolarizing muscle relaxants (Meyers, Singer and Otto, 1980), although this method, as with self-taming, does not prevent an increase in intraocular pressure (Meyers et al., 1978; Giala et al., 1979). Dantrolene pretreatment has been used with suxamethonium (Collier, 1979) although this use of dantrolene is controversial (Agoston, 1980). Vitamin C was reported by Gupta and Savant (1971) to be an effective pretreatment, a finding not confirmed by Wood and colleagues (1977). The most notable success of all has been achieved with diazepam pretreatment (Verma, Chatterji and Mathur, 1978; Eisenberg, Balsley and Katz, 1979; Fahmy, Malek and Lappas, 1979). Fahmy and colleagues (1979) reported that pretreatment with diazepam $0.05\,mg\,kg^{-1}$ prevented muscle fasciculations, decreased the frequency of muscle pains and prevented some of the cardiovascular effects and increases of serum potassium and creatine phosphokinase associated with suxamethonium. All but one of these findings (the increase in creatine phosphokinase) were confirmed by Eisenberg, Balsley and Katz (1979). In this respect diazepam is superior to pretreatment with either small doses of suxamethonium or a non-depolarizing muscle relaxant.

(ii) Muscle pain after operation. The mechanism of postoperative muscle pain after suxamethonium is not entirely clear. Many theories have been advanced: irreversible changes in muscle spindles (Rack and Westbury, 1966), lactic acid production (König, 1956), potassium flux (Mayrhofer, 1959), unsynchronized contraction of muscle fibres resulting in a shearing force on connective tissue (Waters and Mapleson, 1971) or electrolyte imbalance (Collier, 1978).

(iii) Hyperkalaemia. The danger of circulatory collapse following suxamethonium was not recognized until about 8 years after its clinical introduction (Forrest, 1959), and the link with hyperkalaemia in burn patients was not established for another 3 years (Finer and Nylén, 1961). Finer and Nylén (1961) noted that the risk of cardiac arrest was 10 times greater in burn patients than in other patients. Schaner and colleagues (1969) reported that serum potassium concentrations increased by as much as $6\,mmol\,litre^{-1}$ compared with the usual increase of $0.5\,mmol\,litre^{-1}$ or less (Paton, 1959). Patients with nerve injury or nerve disease have also been shown to be at greater risk following suxamethonium than other patients (Roth and Wüthrich, 1969). Insight into this effect is provided by the observation that a hyperkalaemic response to suxamethonium is rarely seen immediately after injury or up to 20 days later (Kopriva et al., 1971). This period of time approximately parallels the time required for muscle cells to become hypersensitive to depolarization following denervation. In these muscles depolarization, which is normally confined to the end-plate, occurs along the whole length of the muscle fibre (Axelsson and Thesleff, 1959). These workers also demonstrated a greatly increased membrane permeability to sodium and potassium ions. It therefore appears that, when widespread muscle depolarization is produced by

suxamethonium, a far greater potassium efflux transpires in burn patients and patients with nerve damage, resulting in hyperkalaemia and the attendant risk of cardiac arrest. As mentioned above, pretreatment with diazepam may decrease the hyperkalaemic response in normal patients, but the effect of diazepam on the hyperkalaemia produced in burn patients by suxamethonium is not yet known.

(iv) Increased intraocular pressure. In man the extraocular muscles contain multiply-innervated muscle fibres in addition to the usually singly innervated fibres. Multiply-innervated muscle fibres respond to depolarization by sustained contracture rather than paralysis and Eakins and Katz (1966) demonstrated a direct dose–response relationship for the contracture of the extraocular muscles of the cat produced by suxamethonium and also showed this response to be blocked by tubocurarine. Patients undergoing ophthalmic procedures are likely to be at risk from increased intraocular pressure and Dillon and colleagues (1957) reported a case of extrusion of ocular contents following suxamethonium. Hexafluorenium (Katz, Eakins and Lord, 1968) and acetazolamide (Carballo, 1965) are two agents which have been used to decrease or prevent a suxamethonium-induced increase in intraocular pressure. However, as Meyer, Singer and Otto (1980) point out, extrusion of ocular contents can occur as a result of sudden force even when the intraocular pressure in zero, if the eye is open.

(v) Increased intragastric pressure. As described above, this effect may be directly related to the degree of muscle fasciculation caused by suxamethonium and pretreatment with either a non-depolarizing muscle relaxant or lignocaine effectively decreases both the fasciculations and the increased gastric pressure (Miller and Way, 1971). A far lesser increase in intragastric pressure is observed in children (Salem, Wong and Lin, 1972).

(vi) Cardiovascular effects. The predominant cardiovascular effects of suxamethonium are a slight increase of mean arterial pressure and bradycardia with repetitive administrations (Graf, Ström and Wåhlin, 1963). The effect of suxamethonium on heart rate differs between children and adults. In children bradycardia is often seen following the first dose of suxamethonium. In adults tachycardia or bradycardia may be seen after the first dose of suxamethonium; however the second dose, if given 15–20 min after the first, often causes bradycardia regardless of the age of the patient (Lupprian and Churchill-Davidson, 1960). The mechanism of bradycardia is not entirely clear; the bradycardia can be blocked clinically by atropine as well as by the ganglion blocking agent trimethaphan camsylate (Arfonad), suggesting that the effect of suxamethonium on the heart is mediated via parasympathetic nerves (Williams et al., 1961). Schoenstadt and Whitcher (1963) suggested that the choline produced by the metabolism of suxamethonium (fig. 5) is responsible for sensitizing the heart to further administrations of suxamethonium. Recently, Sørensen and others (1980) compared the protection afforded by i.v. atropine 9 $\mu g\,kg^{-1}$ with glycopyrrolate 4.5 and 8 $\mu g\,kg^{-1}$ and found both drugs to give adequate protection against suxamethonium-induced bradycardia in patients.

Clinical perspective. There are many anaesthetists who regularly precede the injection of suxamethonium with a small dose of a non-depolarizing agent for both elective patients and for patients with "full stomachs". There is also a large number of anaesthetists who do not pretreat. We could fill many pages with the pros and cons of "pretreatment" with small doses of non-depolarizing agents and still not change the opinions of many people. Thus we let the matter rest by stating that we do not recommend "pre-treating". We know of no evidence which conclusively demonstrates that either "pretreatment" or lack of it is better. In the absence of evidence it is our philosophical decision to recommend not to pretreat. We do, however, pretreat patients at high risk for muscle pain with diazepam.

Complications

Malignant hyperthermia (hyperpyrexia) is a rarely encountered inherent hypersensitivity to suxamethonium (or halothane, or both) (Relton, Britt and Steward, 1973). It occurs in 1 : 50 00–1 : 100 000 cases (Stephen, 1977) and is preceded by tachypnoea, tachycardia, hypermetabolism, arrhythmia and increased temperature and sometimes muscle rigidity (Bronstein et al., 1979). The episode itself can occur anywhere between immediately during surgery (Stephen, 1967) and in the period after operation (Britt and Kalow, 1970). The crisis, once triggered, proceeds with alarming progress and death from cardiac arrest results in 30–40% of cases and body temperature may be found to be 39–42 °C (Stephen, 1975). Other signs include respiratory and metabolic acidosis, hypoxaemia, hyperkalaemia and increased creatine phosphokinase concentrations (Bronstein et al., 1979). Muscular rigidity may be absent in about 25% of cases (Relton, Britt and Steward, 1973). The exact mechanism of malignant hyperthermia is not fully understood, although an intracellular accumulation of calcium during the episode is known to occur (Britt, 1974). Dantrolene sodium, an agent which decreases the calcium influx into muscle cells during depolarization (Putney and Bianchi, 1974), has been reported to be effective in the treatment of malignant hyperthermia (Bronstein et al., 1979). While there is controversy as to whether to pretreat patients susceptible to malignant hyperthermia with dantrolene sodium, there is no question that dantrolene in parenteral form should be available to every hospital in which surgery takes place. I.v. dantrolene sodium is life-saving in the patient experiencing malignant hyperthermia. It is our belief that oral treatment with dantrolene before surgery is not indicated, since dantrolene does produce some side-effects (Pinder et al., 1977) and is not 100% effective. We recommend avoiding agents known to trigger malignant hyperthermia and to have i.v. dantrolene sodium available if a malignant hyperthermic episode is seen.

Myotonia congenita from suxamethonium may at first be mistaken for malignant hyperthermia. This syndrome is the result of disease states of the muscle cells which can result in hyperexcitability and contracture in response to stimulation; both myotonia congenita and dystrophica are thought to be involved. Symptoms include intense local or generalized muscle contracture (Talmage and McKechnie, 1959) which can continue even if the suxamethonium administration is discontinued. The myotonic response may prevent or make difficult adequate ventilation. Limited experience with two patients (R.L.K.) showed that tubocurarine in doses of 15 and 30 mg counteracted the myotonic response.

Myoglobinuria is fortunately a rare complication of suxamethonium. The mechanism of this effect is unknown and case reports are few (Walts, 1975).

CONCLUSIONS

Suxamethonium has undoubtedly been the most widely used muscle relaxant during surgery and will for a while continue to have a place in the anaesthetist's armamentarium. Many authors have, in the past, optimistically looked for a replacement for suxamethonium because of its disadvantages. Whilst there is no non-depolarizing muscle relaxant with an action as brief as that of suxamethonium on the horizon, there are several undergoing clinical trials which may replace the use of suxamethonium in many situations in which previously it was the only choice.

It is to be hoped that future years see a gradual decline of the use of suxamethonium with accompanying benefit to the patient.

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CLINICAL ASSESSMENT OF NEUROMUSCULAR TRANSMISSION

J. VIBY-MOGENSEN

Traditionally, the degree of neuromuscular blockade during and after anaesthesia is evaluated solely on clinical criteria such as muscle tone, the occurrence of spontaneous muscular movements, the "feel" of the anaesthetic reservoir bag, the inspiratory force, and the ability to open the eyes and to raise the head. In the course of time, however, many anaesthetists have put forward convincing arguments for the use of nerve stimulators to assess objectively the neuromuscular function during anaesthesia (Christie and Churchill-Davidson, 1958; Katz, 1970; Ali and Savarese, 1976). Nevertheless, the use of nerve stimulators is still more the exception than the rule in the majority of anaesthetic departments. A very obvious explanation might be that such a practice is actually unnecessary! In other words—and in the words of others—"One manages quite well without it, so why go to the trouble?". But does one manage quite well? And is it so troublesome?

In this article I shall try to answer the following questions: *Why, how* and *when* should the neuromuscular function be monitored during anaesthesia?

WHY MONITOR NEUROMUSCULAR FUNCTION?

As already mentioned, a common argument against the use of nerve stimulators is that they are simply unnecessary. I have no doubt that an experienced anaesthetist can evaluate the degree of neuromuscular blockade in a reassuring way without the use of a nerve stimulator, just as he would be able to anaesthetize a cardiac patient in poor condition without an e.c.g., a CVP-catheter or a Swan–Ganz catheter. However, the question is not how little an experienced anaesthetist can manage with, but rather how we can most easily ensure that *all* patients receive optimal treatment.

In a study of the frequency of residual curarization at three Copenhagen University Hospitals (Viby-Mogensen, Chræmmer-Jørgensen and Ørding, 1979) we found that 24% of the patients were unable to sustain head lift for 5 s on arrival at the recovery room, and 42% had a train-of-four ratio of less than 0.7 (a train-of-four ratio normally taken to reflect adequate recovery; Brand et al., 1977). Of the total of 72 patients examined, none had been monitored with a nerve stimulator before or after operation. Thus in the day-to-day work, the clinical evaluation is apparently not always adequate; but what is the explanation of this? Three factors play a decisive role: the great variation in individual sensitivity to myoneural blocking drugs; the margin of safety of the neuromuscular end-plate; and finally the important relationship between the degree of non-depolarizing neuromuscular block and the effect of an anticholinesterase drug (neostigmine, for example).

The individual difference in sensitivity to myoneural blocking drugs holds for both the depolarizing and the non-depolarizing drugs, but apart from the rare genetic defects in plasma cholinesterase, these differences are of greatest practical significance in the case of the non-depolarizing drugs. Thus, Katz (1967) found that, in a group of patients who received an i.v. injection of tubocurarine 0.1 mg kg^{-1}, the twitch height was unaffected in 6% of the patients, while 7% of the patients experienced total relaxation (100% twitch depression)! Varying degrees of neuromuscular blockade were found in the remaining 87% of the patients. Circumstances are further complicated by the fact that the number of receptors in the neuromuscular end-plate by far exceeds the number required to trigger a muscle action potential under normal conditions; a margin of safety exists. Thus, even with normal inspiratory force and vital capacity, sustained head lift for 5 s, etc., 75–80% of all receptors can still be occupied by the neuromuscular blocker (Waud and Waud, 1971; Ali et al., 1975; Miller, 1976).

If the neuromuscular function is monitored it is possible to antagonize a pancuronium-induced

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neuromuscular blockade in almost all patients by an i.v. injection of neostigmine 2.5 mg (Katz, 1971). On the other hand, if the patient is evaluated on the basis of clinical criteria alone, it may be necessary to give about 40% of the patients more than 2.5 mg of neostigmine for antagonism—and in some of these patients it will still not be possible to produce sufficient reversal (Viby-Mogensen, Chræmmer-Jørgensen and Ørding, 1979). One reason for this is that the clinical effect of neostigmine depends on the degree of neuromuscular block at the time of the injection (Katz, 1971). At a twitch height which is 20% or more of the control twitch height, it is thus normally possible to antagonize the block in the course of 3–14 min. If the twitch height is less than 20%, restitution takes 8–29 min (Katz, 1971). Furthermore, it can be expected that recovery may take longer when reversal of an even more pronounced neuromuscular block is attempted. When the patient is evaluated without a nerve stimulator the actual degree of neuromuscular block in the individual patient at the time of attempted reversal is often a matter of speculation (Viby-Mogensen, Chræmmer-Jørgensen and Ørding, 1979).

Routine use of a nerve stimulator makes it possible to achieve precise individual dosage of both the myoneural blocking drugs and their antagonists. In addition there are specific clinical situations in which nerve stimulators can provide information which is more difficult to obtain or which can not be obtained at all by means of a clinical evaluation. This is the case in the presence of prolonged apnoea after suxamethonium, in the evaluation of deeper degrees of non-depolarizing neuromuscular blockade by using tetanic stimulation (see later), and in the differential diagnosis of respiratory depression after operation. Finally, our experience shows that the nerve stimulator is a valuable help in training and teaching the rational use of myoneural blocking drugs.

PRINCIPLES OF NERVE STIMULATION

Reaction of muscles to nerve stimulation

With intact neuromuscular transmission, electrical stimulation of a motor nerve will result in contraction of those muscles supplied by the nerve. The reaction of the single muscle fibre to a stimulus follows an all-or-nothing law; that is there is maximum contraction of the muscle fibre if the stimulus intensity exceeds a certain threshold. The augmented force of muscle contraction is graded by and is proportional to the number of muscle fibres activated. If the motor nerve is stimulated with sufficient intensity, all the muscle fibres supplied by the nerve will contract. The maximum force of contraction is thereby triggered. If the intensity of the stimulus is increased further the stimulus is described as being *supramaximal.*

Following administration of a myoneural blocking drug, the force of muscle contraction will be reduced. The measured reduction in contraction force at unchanged supramaximal stimulation is an expression of the degree of neuromuscular block.

Clinical types of neuromuscular blockade

In clinical practice it is traditional to consider three different types of neuromuscular blockade.

Non-depolarizing block (induced, for example, by tubocurarine, gallamine and pancuronium), in which the neuromuscular blocker binds to the receptors of the muscle end-plate region. Reversal of this block is achieved with a cholinesterase-inhibiting drug, for example neostigmine.

Depolarizing block (induced, for example, by suxamethonium), in which the neuromuscular end-plate is depolarized by the myoneural blocking drug.

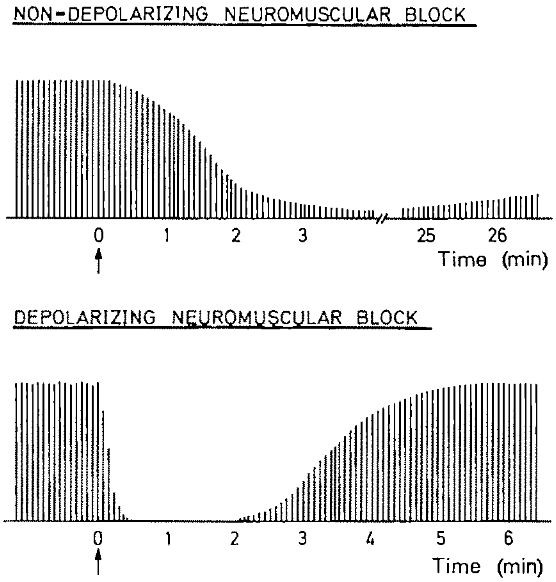
Phase II block (dual block or desensitizing block). This type of block occurs in normal patients when the muscle end-plate has been under the influence of a depolarizing drug over a prolonged period. The original depolarizing block then alters character in the direction of a non-depolarizing block (Churchill-Davidson, Christie and Wise, 1960; Lee, 1975; Ramsey et al., 1980). In patients with genotypically abnormal plasma cholinesterase, a phase II block may be observed following an otherwise normal dose of suxamethonium (Savarese et al., 1975; Viby-Mogensen, 1981a, b).

As will be seen from the following, these three types of neuromuscular block react differently to different types of nerve stimulation.

Clinical methods of nerve stimulation

There are three commonly used types of stimulation:

Single twitch stimulation (fig. 1). Single supramaximal current impulses (often 10–20%


NON-DEPOLARIZING NEUROMUSCULAR BLOCK

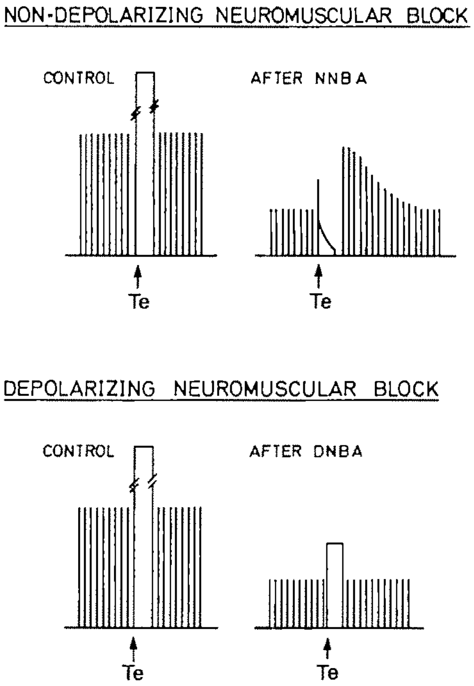
DEPOLARIZING NEUROMUSCULAR BLOCK

FIG. 1. Diagrammatic illustration of the evoked response to single twitch stimulation following injection of a non-depolarizing (upper panel) and a depolarizing myoneural blocking drug (lower panel). Arrows indicate injection of myoneural blocker.

greater than the intensity needed to evoke the maximal response) are applied at greater or smaller intervals (0.1–1.0 Hz). The response to single twitch stimulation depends on the frequency with which the individual stimuli are applied. If the rate of delivery is increased to more than 0.15–0.1 Hz, the evoked response gradually decreases and settles at a lower level (Ali and Savarese, 1977; Lee and Katz, 1980). The impulses should be rectangular or quadratic, with a duration of 0.2 ms or less in order to avoid repetitive nerve firing (Epstein et al., 1969; Epstein and Jackson, 1970).

Tetanic stimulation (fig. 2). The stimuli follow each other at a very rapid rate (e.g. 30, 50 or 100 Hz). In clinical practice today the frequency most commonly used is 50 Hz (for 5 s), because a 50-Hz tetanic stimulation stresses the neuromuscular function to the same extent as does a maximal voluntary effort (Merton, 1954).

At the start of a tetanic stimulation, large amounts of acetylcholine are released from the immediately available stores in the nerve terminal. As these stores become depleted, the rate of acetylcholine release decreases until there is equilibrium between the mobilization and the synthesis of acetylcholine. In spite of this the strength of the mechanical response caused by a tetanic stimulation at for example 50 Hz is maintained in the presence of normal neuromuscular function, because the release of acetylcholine is many times greater than is necessary to evoke a response. There thus exists a wide margin of safety (Paton and Waud, 1967; Gissen and Katz, 1969). When this margin is reduced by a neuromuscular blocker the decrease in the acetylcholine release during tetanic stimulation will result in the development of fade (fig. 2). The degree of fade depends on the extent of the block, on the frequency and duration of the tetanic stimulation, and on how often the latter is applied (Gissen and Katz, 1969; Ali, Utting and Gray, 1970; Stanec et al., 1978).


NON-DEPOLARIZING NEUROMUSCULAR BLOCK

DEPOLARIZING NEUROMUSCULAR BLOCK

FIG. 2. Diagrammatic illustration of the evoked response to tetanic and post-tetanic twitch stimulation following injection of a non-depolarizing (upper panel) and a depolarizing myoneural blocking drug (lower panel). Te = tetanic stimulation (50 Hz for 5 s); NNBA = non-depolarizing neuromuscular blocking agent; DNBA = depolarizing neuromuscular blocking agent. See text for further explanation.

Tetanic stimulation is often combined with single stimuli, applied both before and after the tetanus. The mobilization and synthesis of acetylcholine remain increased for some time after the tetanic stimulation. This explains the increased post-tetanic twitch response (post-tetanic facilitation (PTF), post-tetanic potentiation) which is observed in non-depolarizing blockade (fig. 2). PTF usually declines in the course of a few minutes, as the release of acetylcholine returns to the pretetanic level.

In mechanical recordings, in contrast to recordings of the summated muscle action potential, it is possible to observe both tetanic fade and PTF in spite of normal neuromuscular function, depending among other factors on the frequency and duration of the tetanic stimulus (Epstein and Epstein, 1973; Stanec et al., 1978). Mechanical measurement of PTF is therefore normally considered to be of little help in detecting slight to moderate neuromuscular blockade.

A disadvantage of tetanic stimulation is the fact that it is painful and therefore not acceptable to an un-anaesthetized patient. Further, under certain conditions tetanic stimulation in itself influences the course of the neuromuscular block in the investigated muscle (decurarizing effect) (Feldman and Tyrrell, 1970).

Train-of-four nerve stimulation (fig. 3). Ali, Utting and Gray (1970, 1971a, b) have suggested that the classic types of stimulation should be replaced by train-of-four (TOF) nerve stimulation. In TOF, stimulation is performed by means of four supramaximal stimuli at intervals of 0.5 s over a period of 2 s (2 Hz). The TOF stimuli are repeated every 10–12 s. The amplitude of the fourth response in relation to the first gives the *train-of-four ratio*.

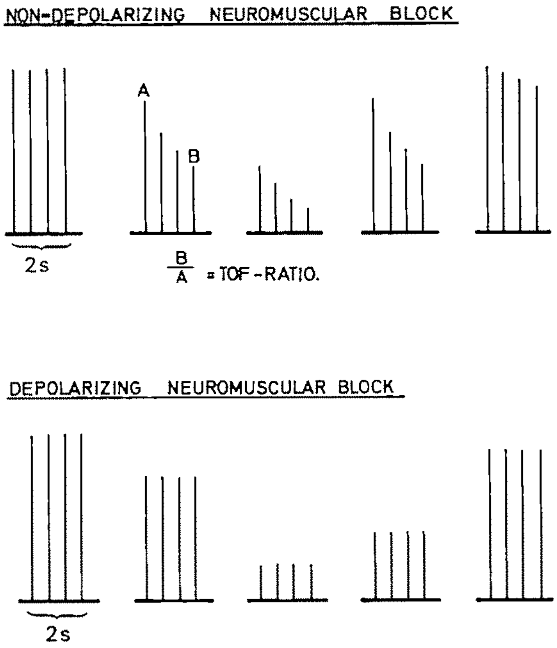

NON-DEPOLARIZING NEUROMUSCULAR BLOCK
A
B
2s
B/A = TOF-RATIO.
DEPOLARIZING NEUROMUSCULAR BLOCK
2s

FIG. 3. Diagrammatic illustration of the evoked response to train-of-four (TOF) nerve stimulation following injection of a non-depolarizing (upper curve) and a depolarizing myoneural blocking agent (lower curve). Note "fade" in the TOF response during partial non-depolarizing neuromuscular blockade.

During a non-depolarizing block this ratio is reduced, and within certain limits is inversely proportional to the degree of neuromuscular block (fig. 4). During a depolarizing block, all four

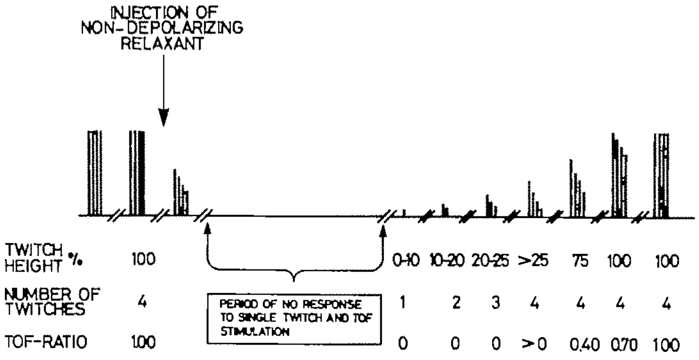


FIG. 4. Diagrammatic illustration of the relationship between the evoked responses to single twitch (0.1 Hz) and train-of-four (TOF) nerve stimulation during a non-depolarizing neuromuscular blockade. This relationship differs during spontaneous and induced recovery (Ali et al., 1981). To mimic the normal clinical situation the relationship during spontaneous recovery is shown until 25% recovery of twitch height (Lee, 1975). In contrast, the relationship given for twitch heights above 25% is valid during induced recovery with a cholinesterase inhibitor (Ali et al., 1981). Note the "period of no response" to either of the two stimulation forms. This period of intense neuromuscular blockade may be evaluated using tetanic and post-tetanic single twitch stimulation (see text for further explanation).

twitch heights will ideally be of equal height (TOF ratio 0.9–1.0). Everything else being equal, a decreasing TOF ratio during a depolarizing block signifies that a phase II block is under development.

The advantages of using TOF stimulation are greatest in non-depolarizing block, and when phase II block is suspected, as the degree of block can then be read directly from the TOF ratio even though a preoperative control value may be lacking. For this reason, and because TOF is less painful than tetanic stimulation, this type of stimulation can be used at any time during and after anaesthesia. A further advantage of TOF is that the neuromuscular block remains uninfluenced by the stimulation. Also, in revealing residual curarization its sensitivity is greater than single twitch stimulation or tetanic stimulation of 50 Hz (Ali et al., 1981).

Relation between different methods of stimulation

The least sensitive method in demonstrating a partial neuromuscular block is single twitch stimulation. The twitch response is not reduced before more than 75–80% of the cholinergic receptors in the neuromuscular end-plate are blocked. The response disappears completely when 90% of the receptors are blocked (Waud and Waud, 1971).

The same or possibly a slightly greater sensitivity can be obtained with tetanic stimulation at 30 Hz for 5 s. Greater sensitivity is achieved by tetanic stimulation at higher frequencies. At 100 Hz for 5 s, fade develops already when 50% of the receptors are blocked, and at 200 Hz for 5 s, fade is observed when merely 30% of the receptors are blocked (Gissen and Katz, 1969; Waud and Waud, 1971).

With TOF, the TOF ratio begins to decrease when more than 70–75% of the receptors are blocked (Waud and Waud, 1972).

When a non-depolarizing block is developing, the following relation exists between the reaction to TOF and the single twitch response: the response to the fourth stimulus disappears (TOF ratio = 0) when the height of the first response is about 25% of control. The response to the third stimulus disappears when the height of the first response is about 20% of control, while the response to the second stimulus disappears when the height of the first response is about 10% of control. With reversal of the block, the reappearance of the four twitches is in inverse sequence to their disappearance (Lee, 1975) (fig. 4). At a TOF ratio of 0.70–0.75 (induced recovery) the twitch response will have reached control value, and there will be no fade in the response to a tetanic stimulation of 50 Hz for 5 s (Ali and Kitz, 1973; Ali and Savarese, 1976; Ali et al., 1981).

Intense non-depolarizing neuromuscular blockade cannot be evaluated using single twitch stimulation or TOF nerve stimulation. Thus, during halothane anaesthesia, injection of pancuronium 0.1 mg kg^{-1} for tracheal intubation causes disappearance of the response to single twitch stimulation and TOF stimulation for 20–100 min (fig. 4). During this "period of no response" it is impossible to tell clinically whether the response to TOF stimulation—and hence the possibility of sufficient reversal—will return in say 20, 60, or perhaps 100 min. It is, however, possible to quantify at least a part of this period by applying tetanic stimulation (50 Hz for 5 s) and observing post-tetanic responses (fig. 5). During a pancuronium-induced neuromuscular blockade the response to post-tetanic twitch stimulation appears an average of 36 min before the first reaction to TOF nerve stimulation, and there is a correlation between the maximal post-tetanic twitch height in per cent of control twitch height, and the time to first response to TOF stimulation (Viby-Mogensen, Howardy-Hansen et al., 1981). Evaluation of post-tetanic twitch response in relation to a control twitch response presupposes access to monitoring equipment, whereas the number of post-tetanic twitch responses can simply be counted (the post-tetanic count: PTC). It appears from figure 6 that time until return of response to TOF nerve stimulation is related to the number of post-tetanic twitch responses present (PTC) at any given time.

CLINICAL MONITORING OF NEUROMUSCULAR FUNCTION

Nerve stimulators for clinical use

Several nerve stimulators for clinical use are commercially available (Churchill-Davidson, 1965; Katz, 1965a; Zeh and Katz, 1978; Crul et al., 1980; Viby-Mogensen et al., 1980). In my opinion it is not so important which stimulator is used, the important thing is to know its characteristics! For instance, the response to tetanic stimulation and the degree of PTF are

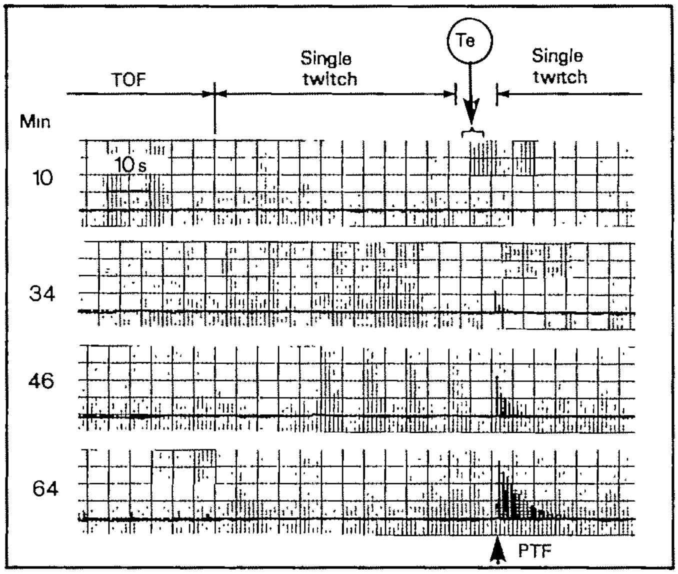


FIG. 5. Post-tetanic facilitation (PTF) during intense neuromuscular blockade following pancuronium $0.1\ mg\ kg^{-1}$ (halothane anaesthesia). Basically train-of-four (TOF) nerve stimulation was used, but 10, 34, 46 and 64 min after the injection of pancuronium the mode of stimulation was changed to 1.0 Hz single-twitch stimulation. After 1 min a tetanic stimulus (50 Hz) was applied for 5 s (Te). Three seconds later single twitch (1 Hz) was again applied for 1 min followed by TOF nerve stimulation. Ten minutes after injection of pancuronium there was no response to any of the stimulation forms. Thirty-four minutes after the administration of pancuronium there was still no response to TOF, single twitch or tetanic stimulation, but now post-tetanic facilitation was present. Twelve minutes later there was still no response to TOF, single twitch or tetanic stimulation, but the post-tetanic twitch response had increased considerably. Sixty-four minutes after the injection of pancuronium the first response to TOF stimulation appeared, but still there was no reaction to single twitch (1 Hz) or tetanic stimulation. The post-tetanic twitch response had increased further.

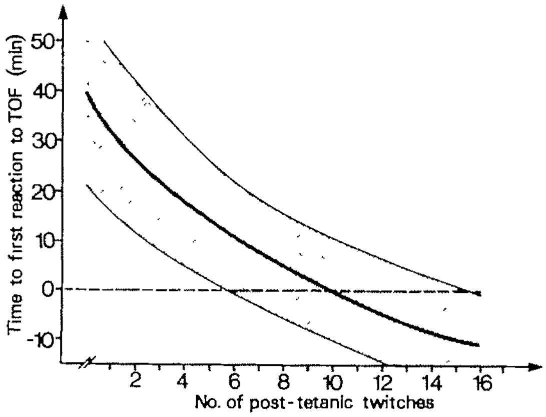


FIG. 6. Relationship between minutes to first reaction to train-of-four (TOF) and number of post-tetanic twitches (the post-tetanic count: PTC) in 17 patients anaesthetized with halothane and given pancuronium $0.1\ mg\ kg^{-1}$ for tracheal intubation. The mean curve and 95% prediction region are shown (Viby-Mogensen, Howardy-Hansen et al., 1981).

dependent on the frequency of the tetanic stimulus, the duration of that stimulus and the time lapse between the conclusion of the tetanic stimulus and the first post-tetanic single stimulus. It is therefore of importance that these variables be held constant, if a valid comparison is to be made between the neuromuscular responses to tetanic stimulation at different times during anaesthesia. We use the Myotest nerve stimulator (Viby-Mogensen et al., 1980) (fig. 7). This stimulator gives a unipolar constant-current impulse, with an adjustable amplitude from 0 to 40 mA (the latest version gives up to 60 mA) and with a constant impulse duration of 0.2 ms. The constant-current impulse means that, irrespective of changes in impedance between the electrodes, the current to the stimulated nerve will be unchanged. The stimulator offers the following stimulation forms: 1.0- and 0.1-Hz single twitch stimulation, TOF nerve stimulation, and 50-Hz tetanic stimulation for 5 s followed by a 3-s pause before returning to single twitch stimulation. A stimulation frequency of 0.1 Hz allows the greatest possible response to a single stimulus. The 1.0 Hz frequency makes it easier to elicit the

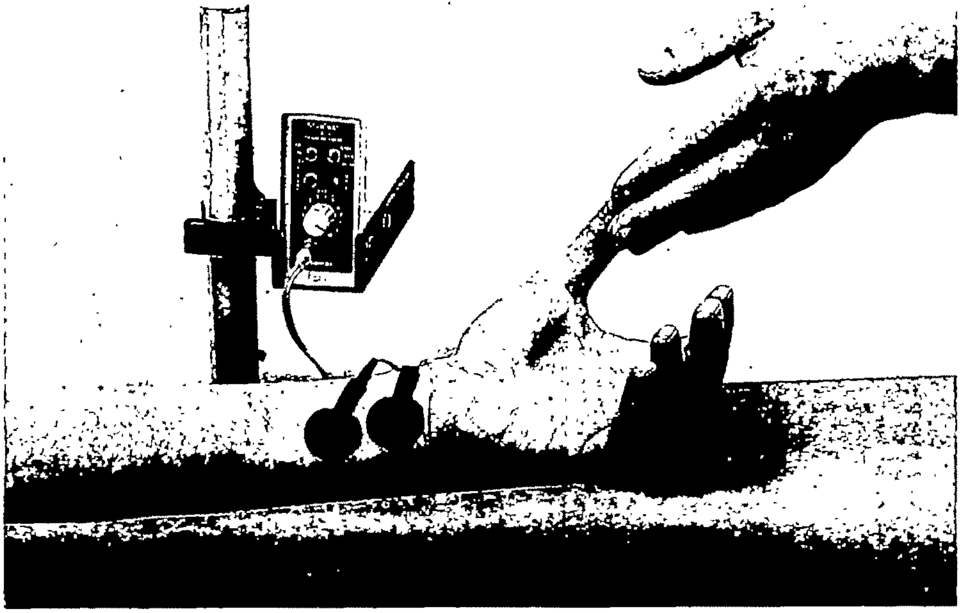


FIG. 7. Monitoring of neuromuscular blockade without recording equipment. A Myotest nerve stimulator and surface electrodes are used. The evoked response is determined by tactile evaluation.

necessary supramaximal intensity in a shorter time and may be used (in combination with a 50-Hz tetanic stimulus for 5 s) in the evaluation of an intense non-depolarizing neuromuscular blockade (Viby-Mogensen, Howardy-Hansen et al., 1981).

Transmission of impulses from stimulator to nerve

Both surface and needle electrodes can be used.

Surface electrodes. A set of non-disposable surface electrodes (conducting rubber) may be delivered with the nerve stimulator, but disposable electrodes, as e.c.g. electrodes, can also be used. After careful cleansing of the skin, the electrodes are placed, for example, over the ulnar nerve at the volar side of the wrist (fig. 7). The distal electrode is placed about 1 cm proximal to the point where the proximal flexion crease of the wrist crosses the radial side of the tendon to the ulnar flexor carpi muscle. The proximal electrode can be placed either 2–3 cm proximal to the distal electrode (preferably on the other side of the nerve) or over the ulnar nerve at the elbow. The placing of the electrodes is very important. Small displacements may result in considerable changes in stimulation current requirements. Furthermore, the electrodes must be so placed that nerve and not muscle is stimulated.

As the stimulation pulses are monophasic, interchanging the electrode connections (exchange + with −) may sometimes increase the stimulation considerably.

Needle electrodes. In some cases—particularly in obese patients and in patients with very cold extremities—surface stimulation at the supramaximal level is not possible. In these cases needle electrodes should be used. The needles should be placed subcutaneously and not in the nerve. If the patient is awake this is best done with local analgesia. The needle electrodes must be held in place with tape, as movements of the needle tips may influence monitoring.

Special needle electrodes for nerve stimulation are commercially available, but ordinary steel injection needles may also be used.

Evaluation of the evoked response

In principle, it is possible to stimulate any superficially placed, peripheral motor nerve and evaluate the response to this stimulation. In the clinic, however, it is most often convenient to stimulate the ulnar nerve, and the evoked response can then be evaluated visually, by touch, mechanically or electrically (by electromyography).

Visual evaluation. The arm is placed in 90° abduction with the hand in supination (fig. 7).

Using single stimuli, the movements of the thumb are evaluated and compared, if possible, with the control value.

In TOF stimulation, the primary observation is the count of the number of responses to the TOF stimulation, since as already mentioned there is a relationship between the number of visible finger movements and the degree of the neuromuscular block (Lee, 1975) (fig. 4). If there is a reaction to all four stimuli, an estimation of the magnitude of the fourth deflection in relation to that of the first can be attempted (TOF ratio). This, however, is difficult, especially for an untrained person. On a visual basis it is often impossible to decide whether the TOF ratio is 0.4, 0.7, or perhaps 1.0 (Savarese and Ali, 1977). On the other hand, there is no fade in a tetanic response (50 Hz for 5 s) when TOF ratio is greater than 0.7 (Ali et al., 1981) and it is normally easy visually to decide whether there is fade in a tetanic response.

Tactile evaluation. With one's hand resting loosely in the patient's hand, or better still with the finger tips resting lightly on the patient's thumb in slight abduction (fig. 7), it is often possible to get a better impression of the force of contraction than can be obtained visually. In addition, there is no risk of direct nerve stimulation of the muscles of the thumb, which could be the case with the 4th and 5th finger. It is easy to decide by touch if there is any reaction to TOF stimulation and how many responses are present. Even by touch, however, it is difficult to estimate the TOF ratio when all four responses are present. The only way in which one can be sure by touch that the patient has reached sufficient reversal at the end of surgery, is by evaluating the patient's reaction to a tetanic stimulation (50 Hz for 5 s).

Deeper degrees of neuromuscular blockade—that is when there is no reaction to single twitch (0.1 Hz) or TOF stimulation—can also be evaluated by touch, as there is a relationship between the number of post-tetanic reactions recognizable by touch and the time to first reaction to TOF stimulation. However, studies still in progress suggest that the curve expressing the relationship between the number of post-tetanic twitches and the time to the first reaction to TOF has a somewhat steeper course when the number of post-tetanic twitches is evaluated by touch, than when the number is counted from a recorder (fig. 6).

Mechanical measurements. In order to obtain a more exact measurement of muscular reaction to the nerve stimulation, the tension developed in the muscle can be measured. A condition for correct and reproducible measurements is that the contractions are isometric. This presupposes that it is possible to apply (and maintain) a preload. In clinical practice this is most easily achieved by making measurements on the thumb using a preload of 100–300 g. In addition, as the adductor pollicis muscle is the only muscle in the thumb innervated by the ulnar nerve, measurements on this digit are about the nearest one can come to *in vitro* investigation in the clinic. The principle is that the thumb acts on a force–displacement transducer, whereby the force of contraction is converted into an electrical signal, which via an amplifier can be presented on a screen or in a write-out on a paper strip, or both.

For several years we have used a specially constructed armboard, on which the arm is placed in abduction and pronation, so that the four ulnar fingers grasp the armboard and the thumb acts on the rigidly fixed transducer (Statham UC 3, gold cell) (fig. 8). The armboard is mounted on a ball-head attached to the operating table. The advantages of this system are primarily that it can be assembled in a few minutes, that it is stable in every-day use, and that it can be manufactured in any department of anaesthesia without great expense. A disadvantage of the system is that the hand lies in pronation. This may cause trouble in placing the electrodes to achieve a supramaximal response, because the electrodes may be displaced when the hand is turned. In collaboration with a Danish firm (Biometer), therefore, we have developed a new armboard ("The Herlev armboard"), and a new transducer (fig. 9). With this the arm is placed in supination on a vacuum cushion filled with plastic balls. When the cushion has been modelled in accordance with the patient's arm, the arm is fixed firmly and the cushion evacuated for air. The thumb is then placed in a ring fastened to the transducer. This is placed in a special holder which allows the

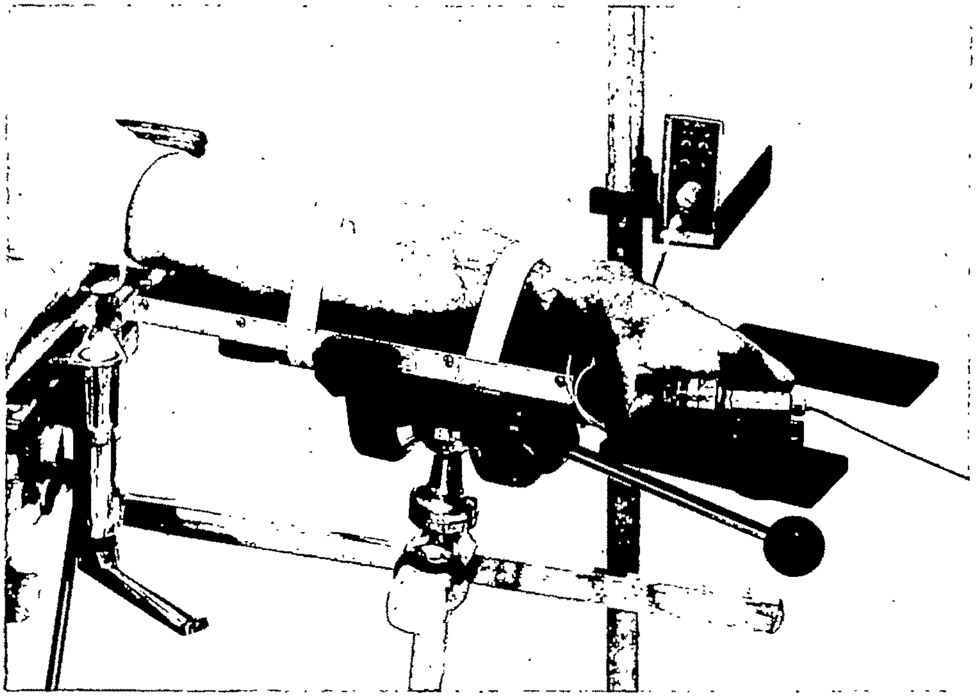


FIG. 8. A specially constructed armboard for mechanical measurements of evoked responses. The force–displacement transducer (Statham UC 3, Gold cell) is mounted on the armboard by a screw (not shown in the picture) allowing a preload to be set and the transducer to be moved in any direction in the horizontal plane. The armboard itself, which is attached to the operating table, can be moved in any desired direction.

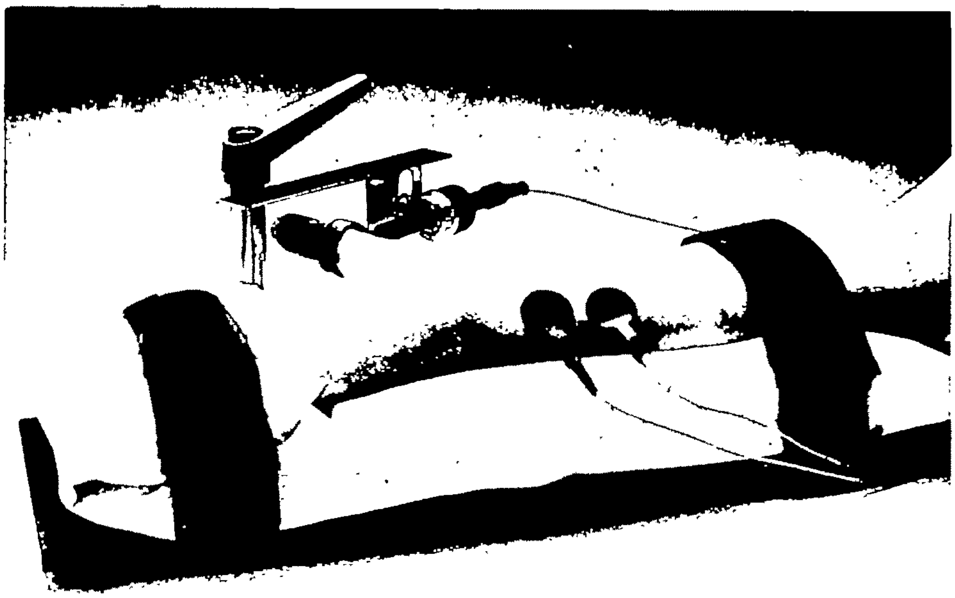


FIG. 9. The "Herlev armboard" for mechanical measurements of evoked responses. See text for further explanation.

transducer to be so suspended that the thumb always applies tension exactly along the length of the transducer. A screw placed behind the transducer makes it possible to adjust and record preload at any time. The transducer is made of plastic and has a capacity of up to 15 kg. This avoids problems of overloaded transducers which have been described (Freund and Merati, 1973). The armboard, with an accompanying neuromuscular transmission analyser and recorder (see later) is now commercially available in most European countries.

Besides the methods described here for mechanical recording of the evoked response, numerous others have been published (Katz, 1965b; Tyrrell, 1969; Baraka, 1973; Walts, 1973; Ali and Savarese, 1976; Armstrong, Goat and Loach, 1977; Crul, 1980; Stanec et al., 1980). No matter which method is used, however, it is important, first that the transducer is placed correctly in relation to the muscle in which the measurements are being made (Epstein and Epstein, 1975), second that a preload is used and maintained (Donlon, Savarese and Ali, 1979), and finally that the transducer used is not overloaded (Freund and Merati, 1973).

Electromyographic measurements. It is also possible to monitor the neuromuscular function by electromyography (e.m.g.). In this method the evoked compound action potential is registered from the muscle via two surface or needle electrodes (in most cases the adductor pollicis brevis or the abductor digiti minimi). The active electrode is usually placed over the motor point of the muscle and the indifferent electrode over the tendon of insertion of the muscle. The ground electrode, which it is advantageous to have larger than the lead-off electrodes, can then be interposed between the stimulating and recording electrodes. The compound e.m.g. evoked by the nerve stimulation is collected by the recording electrodes and transmitted via an amplifier to an oscilloscope, for example.

In principle, recording the electromyographic response to nerve stimulation is preferable to the mechanical twitch measurement. In particular, only changes in the neuromuscular end-plate are measured on the e.m.g. In mechanical recording the tension measured depends both on those changes that may have occurred in the neuromuscular end-plate region, and on possible changes in the contractility of the muscle. Further, with e.m.g. recording, in contrast to mechanical recordings, it is possible to measure very rapid changes in the neuromuscular function. Tetanic fade will thus often be more pronounced in e.m.g. recording than in mechanical recording, because it takes some time for the muscle to reach maximal contractility (Epstein and Epstein, 1975). Finally, by using electromyography it may be possible to reduce the problem of transducer fixation already mentioned.

Despite the above, the clinical use of electromyography is still uncommon, although used for research in a number of laboratories. One reason for this is that there are still a number of unsolved technical problems associated with its use. Epstein and Epstein (1975) and Lee and coworkers (1977) are among those who have now described methods allowing a direct transcription of the evoked e.m.g., and quite recently the first apparatus for monitoring based on e.m.g. measurements has become commercially available (Crul et al., 1980). However, it is important to be aware that there may be differences between the electromyographic and the mechanical response (Epstein and Epstein, 1973; Katz, 1973).

For additional information on electromyographic monitoring of neuromuscular transmission see Epstein and Epstein (1975).

Neuromuscular transmission analysers. The different neuromuscular variables such as TOF ratio and twitch height depression are most often calculated manually from the recorded curves. In a number of centres work has been going on for some years developing so-called neuromuscular transmission analysers (Ali and Kitz, 1973; Perry et al., 1975; Lee et al., 1977; Viby-Mogensen, Kann et al., 1981), which automatically calculate these variables, facilitating both the clinical work and the work in research projects. Recently, two such types of apparatus have become commercially available. The one apparatus is based on measurements of the evoked electromyographic response (Crul et al., 1980) and the other (Myograph 2000) on measurements and recordings of the mechanical response (figs 9, 10). We have not had the opportunity to test the first-mentioned instrument, but have been involved in the development and testing of the Myograph. This instrument constitutes the first series-produced apparatus containing all the elements necessary for the mechanical monitoring and

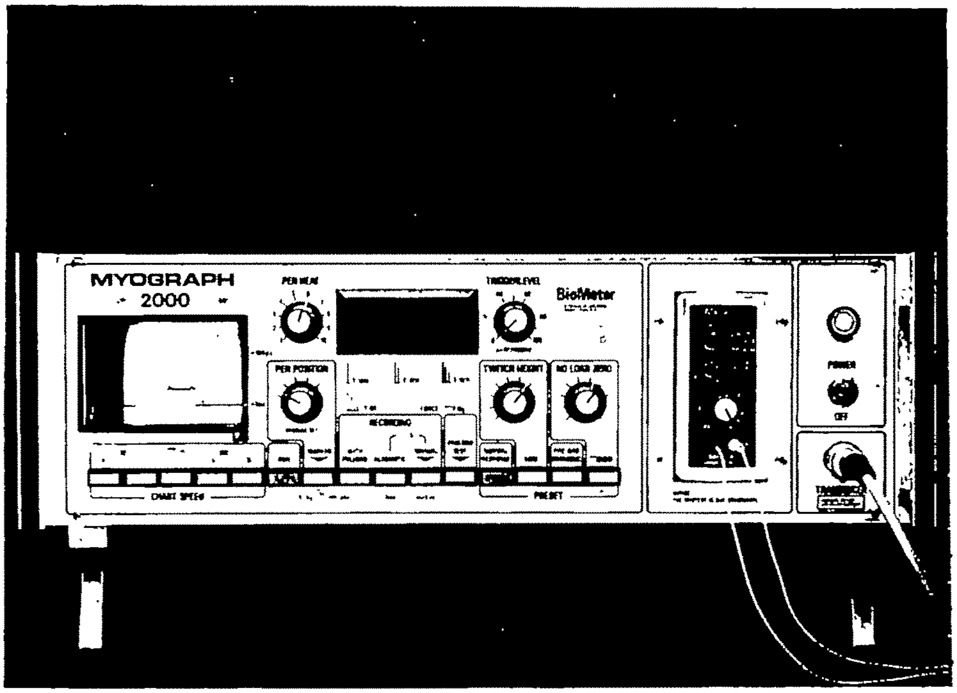


FIG. 10. Myograph 2000, a neuromuscular transmission analyser for mechanical measurements. See text for further explanation.

recording of neuromuscular function: a nerve stimulator, an armboard with transducer, a measuring and calculating unit with digital display and a write-out. Among other things the Myograph allows measurements of the absolute force developed in the thumb in reaction to a nerve stimulation, the control and adjustment of preload at any time during the measurements, and automatic or manual reduction of the amplification when using tetanic stimulation. The display shows the twitch height in per cent of control, the number of responses to TOF or, if all four responses are present, the TOF ratio. Simultaneously, the response is recorded in the write-out permitting continuous control of the calculating unit and documenting material for research work.

CORRELATION BETWEEN EVOKED RESPONSES AND CLINICAL OBSERVATIONS

Single stimulation. A twitch height of 5% or less secures sufficient relaxation of the musculature of the jaw and larynx for laryngoscopy and endotracheal intubation and of the abdominal wall for surgery (Katz, 1971; Ali and Savarese, 1976). The abdominal musculature usually feels tight at twitch heights greater than 25%. The head cannot be lifted from the table before the twitch height is about 90% of the control value (corresponding to a TOF ratio of 0.5–0.6), but even 100% recovery of twitch height does not always indicate normal clinical neuromuscular function (Ali and Savarese, 1976; Ali et al., 1981).

TOF stimulation. The relationship between the reaction to single twitch stimulation and TOF stimulation has already been discussed (fig. 4).

There is a good correlation between TOF ratio and head-lift. At a ratio of 0.4 or less, no patient is able to lift the head from the table. At a ratio of 0.6 the patient is able to sustain head-lift for 3 s (Ali, Utting and Gray, 1971a, b), but vital capacity and inspiratory force will often be reduced (Ali et al., 1975; Brand et al., 1977). A TOF ratio of 0.75 enables the patient to open the eyes widely, protrude the tongue, exhibit cough-sufficiency and sustain head-lift for at least 5 s (Ali and Kitz, 1973; Brand et al., 1977). At a TOF ratio of 0.8 and more, the vital capacity and inspiratory force are normal (Ali et al., 1975).

Tetanic stimulation. Tetanus of 50 Hz for 5 s without fade indicates that the patient is able to maintain a head-lift for 5 s, protrude the tongue, open the eyes, and that vital capacity and maximum voluntary ventilation are at least 90% of control (Walts, Levin and Dillon, 1970; Ali and Kitz, 1973).

PRACTICAL CLINICAL USE OF A NERVE STIMULATOR

During induction of anaesthesia

It is convenient to attach the nerve stimulator before induction of anaesthesia (fig. 7), but normally it should not be switched on until *after* the patient is asleep. When the supramaximal stimulus is reached—and the reaction of the finger to this is known—the myoneural blocking drug is injected.

There are large individual variations in sensitivity to the non-depolarizing neuromuscular blocking drugs (Katz, 1967). By means of the nerve stimulator it is possible, in the individual patient, to determine the dose sufficient to achieve the desired degree of neuromuscular block. If a non-depolarizing neuromuscular blocking drug is administered in small doses until the response to TOF stimulation, evaluated visually, just shows fade (TOF ratio about 0.4), then a doubling of this dose will result in about 80% depression of the twitch height, and tripling the dose will result in about 95% depression (Savarese and Ali, 1977).

During operation

In most situations, a twitch depression of 90–95% will be enough to ensure sufficient muscle relaxation. If the patient is relaxed with a non-depolarizing drug, this means that the reaction to single twitch stimuli (0.1 Hz) can just be seen or felt, and only the response to the first of the four stimulations of TOF can be seen or felt. The advantage of keeping the patient relaxed at this level is above all that antagonism of the postoperative block is facilitated (see later).

On occasion, respiratory movements, cough or hiccup, may occur, even though the twitch height is less than 5–10% of the control twitch height. There are several explanations for this. The respiratory muscles are less sensitive to myoneural blocking drugs than the peripheral muscles (Johansen, Jørgensen and Molbech, 1964; Wymore and Eisele, 1978), and a 95% depression of the twitch height corresponds to only an 80% depression of the tetanic response (Lee and Katz, 1980). Powerful nerve stimulation triggered off by the surgical intervention during a superficial anaesthesia can therefore elicit respiratory movements. Finally, peripheral cooling may reduce the blood flow to the muscle on which measurements are being made. This may result in inhibition of the diffusion of the myoneural blockers away from the neuromuscular end-plates, so that the reversal of the peripheral muscles may "drag after" the reversal of the respiratory muscles.

In continuous infusion of suxamethonium, it may be difficult to adjust the patient to a constant twitch height, because of the rapid breakdown of the drug. In order to achieve a sufficient degree of muscle relaxation it is often necessary that there just is *no* reaction to nerve stimulation. To avoid overdosage it is necessary to stop the infusion at regular intervals or to reduce the rate of infusion of suxamethonium and evaluate the response to nerve stimulation.

During reversal of neuromuscular block

Reversal of the non-depolarizing block by means of a cholinesterase inhibitor should not be started before there is a reaction to single stimuli (0.1 Hz) or TOF. If the reversal is started when only the first response in the TOF is present (corresponding to a twitch height <10%), it will take 10–30 min to reach a TOF ratio of 0.7 (corresponding to 100% recovery of twitch height. If, on the other hand, all four responses to TOF stimulation can be seen or felt (corresponding to a twitch height of at least 25%), reversal of the block should be possible in less than 10 min (Katz, 1971).

Reversal of the depolarizing block normally occurs spontaneously in 5–10 min after the termination of the suxamethonium infusion.

After operation

Even if a nerve stimulator may not have been used during operation, it can be of great diagnostic and therapeutic value after the operation. A TOF ratio greater than 0.7 and absence of fade in the tetanic response (e.g. 50 Hz for 5 s) in a patient with cough- and respiratory-insufficiency, excludes the presence of residual curarization. On the other hand, a low TOF ratio or fade in the tetanic response suggests that the patient still experiences partial relaxation. Treatment of this residual curarization can then be controlled by a nerve stimulator.

WHICH PATIENTS SHOULD BE MONITORED WITH A NERVE STIMULATOR?

A nerve stimulator makes it possible to provide precise, individual dosage of the neuromuscular blocking drugs. This speaks in favour of monitoring all patients during operation. As already mentioned, careful clinical evaluation of the patient during and after operation will often be sufficient to ensure optimal treatment. There is no doubt, however, that patient safety can be considerably increased, if neuromuscular function is monitored during operation in the following patient categories:

(1) Patients with severely reduced kidney or liver function, or both.
(2) Patients in poor general condition.
(3) Patients with severe pulmonary disease.
(4) Patients with severe heart disease or bronchial asthma, in whom achievement of reversal by means of a cholinesterase inhibitor might be problematic.
(5) Patients with neuromuscular disease (monitoring may, however, be unreliable in patients with upper motor neurone lesions (Graham, 1980; Moorthy and Hilgenberg, 1980)).
(6) Severely obese patients.
(7) Patients who have to undergo prolonged surgery (>3–4 h).
(8) Patients in whom relaxation is produced with continuous infusion of suxamethonium.

SUMMARY OF SOME IMPORTANT RULES FOR MONITORING OF NEUROMUSCULAR FUNCTION

Experience shows that, the first time an anaesthetist has to use a nerve stimulator, it is always the same problems that are encountered. Some important rules are summarized below.

Stimulation should be definitely supramaximal (if necessary move the electrodes), and the various forms of stimuli should not be applied too often. The reaction to single-twitch stimulation decreases if stimulation is more frequent than every 6–10 s; TOF must not be applied more frequently than every 10 s; tetanic stimulation not more frequently than every 6–10 min. The reaction to a tetanic stimulus and to post-tetanic twitch stimulation depends both on the duration of the tetanic impulse (1–10 s) and on the frequency (30–200 Hz). Direct muscle stimulation (the response does not appear in spite of total neuromuscular block) can usually be avoided by correct placing of the electrodes and by avoiding too high stimulation intensity.

In mechanical recordings it is important to apply and maintain a preload of 100–300 g, to site and fasten the transducer in the correct position in relation to the muscle on which measurements are to be made, and finally to avoid overloading the transducer. In clinical studies in particular, it is of importance to bear in mind that the reaction to supramaximal single-twitch stimulation increases during the first 8–12 min after commencement of the stimulation.

Without e.m.g. or mechanical recording, *tactile evaluation* of the thumb reaction is normally the best way to evaluate muscle force. No matter how the evaluation is made it is, however, decisive to compare the reaction to nerve stimulation with the clinical condition of the patient. Particularly if the extremities are very cold, there may be a disproportion between the degree of relaxation of the peripheral muscles and that of the respiratory muscles.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LONDON MEETING

NOVEMBER 13, 1981

THE RESPIRATORY DEPRESSION OF EXTRADURAL MORPHINE

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Respiratory depression, usually of delayed onset, has been reported following extradural opiates (Scott and McClure, 1979). While the aetiology, frequency and exact time-course have not yet been defined, some investigators have not encountered this problem (Torda et al., 1980).

We have looked for evidence of respiratory depression by measuring the slope of the carbon dioxide response curve in patients breathing 3% and 6% carbon dioxide in air. The study was undertaken in 21 patients having minor or intermediate operations under bupivacaine lumbar extradural anaesthesia. One hour after the end of operation, the response to carbon dioxide measured and then morphine 2 mg in normal saline 10 ml was given via the extradural cannula. Patients were subsequently nursed supine (11 patients) or semi-sitting (10 patients).

Although there was some respiratory depression immediately following operation, carbon dioxide responses had recovered to near control value by 2 h after morphine administration. However, 4 h after morphine had been given, there was more marked respiratory depression in those patients nursed supine. This persisted at the 8- and 18-h measurements, although recovery was commencing by 24 h. Using the Wilcoxon rank sum test, the reduction in slope was significant ($P<0.05$) at 4, 8 and 18 h compared with the values at 2 h, and at 8 and 18 h compared with control values.

The 10 patients in the semi-sitting position did not show the same pattern of delayed respiratory depression as the supine patients. As a result of large individual variation, the difference between the groups was not significant. One patient exhibited respiratory depression as marked as any in the supine group.

No patient received a second dose of morphine before the 4-h measurement. Two patients in each group received a second dose before 8 h.

These results demonstrate a consistent pattern of detectable respiratory depression commencing at approximately 4–8 h, and continuing until 18–24 h after administration of morphine extradurally to patients subsequently nursed supine. They suggest, but do not yet prove, a protective effect from an upright posture.

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THE DISPOSITION OF PLASMA PETHIDINE IN 10 VOLUNTEERS UNDER CONDITIONS OF VARIED URINARY pH

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Pethidine has been studied extensively in both volunteers and patients. Urinary pH (Chan, 1979) liver disease (Klotz, et al., 1974) age and physico-chemical properties (Chan, 1979) affect the disposition of pethidine. While urinary pH plays an important part in the renal elimination of the unchanged drug and its weakly basic metabolite norpethidine the effect of changes in urinary pH on plasma concentrations of the drug has not been studied.

In the present investigation, this effect has been studied during conditions of uncontrolled and controlled (acidic and alkaline) urinary pH induced and maintained as described previously (Chan, 1979).

Studies were carried out in 10 male volunteer subjects who were fasted overnight. All were healthy Caucasian non-smokers (aged 21–35 yr). Each subject was studied on three different occasions, separated by a period of at least 7 days. A cannula was placed in a superficial vein and kept patent by intermittent infusion of heparinized saline 2 ml. Pethidine hydrochloride, 150 $\mu g\ kg^{-1}$ was injected to a vein of the other fore-arm over a period of not more than 10 s. Blood samples (10 ml) were collected at 0, 2.5, 5, 10, 20, 30 and 60 min, and at 1.5, 2, 4, 6, 12 and 24 h, into heparinized tubes. Plasma samples were removed after centrifugation at 2000 *g* for 15 min and stored at −20°C before analysis using a nitrogen-selective gas–liquid chromatographic procedure (Tse and Chan, 1981). These studies were approved by the Medical Research Ethical Committee.

In all subjects, under all three conditions of urinary pH, there was a rapid decrease in plasma concentration of pethidine between 2.5 and 10 min. The concentration of the drug subsequently declined more slowly, but was detected in plasma in the 10 subjects up to 24 h. Kinetic analysis by computer modelling indicates that pethidine is eliminated from the plasma tri-exponentially in all conditions.

Accurate parameters can best be obtained from the acidic urine condition. Average terminal elimination half-life of the drug is 6.9, 8.1 and 10.7 h for conditions of acidic, uncontrolled and alkaline urinary pH respectively. These half-lives are longer than those reported in studies in which blood sampling was terminated at 6 h after injection. It is likely that these studies missed the terminal elimination phase which is identified in the present investigation.

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ACUTE TOLERANCE OF CARDIOVASCULAR REFLEXES TO FENTANYL IN THE DOG

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The development of chronic tolerance to the effects of opiates is well documented. Acute tolerance has been described in relation to the cardiovascular system only for morphine over a few hours following its i.v. administration (Schmidt and Livingston, 1933; Martin and Eades, 1961). Recently, Colpaert and others (1980) have shown in rats that acute tolerance to the analgesic effects of fentanyl can develop during a period of 4 days.

In order to establish if acute tolerance to fentanyl can develop also during only a few hours, the effect of the i.v. administration of fentanyl on evoked responses of arterial pressure ($\Delta\overline{AP}$) and heart rate (ΔHR) was studied.

Anaesthesia was induced in 12 dogs with methohexitone and maintained with α-chloralose. Neuromuscular blockade was induced and maintained with suxamethonium and the lungs were ventilated artificially via an endotracheal tube.

The radial nerve was exposed, desheathed, cut distally and mounted on silver–silver chloride electrodes in mineral oil. Ten-second trains of supramaximal stimuli (50 V, 0.5 ms, 30 Hz) triggered by the R wave of the e.c.g. were applied to the nerve and the mean arterial pressure and beat-by-beat heart rate were recorded. Plasma concentrations of fentanyl were measured also.

The dogs were allocated randomly to two groups. Group A received a bolus dose of fentanyl 100 μg kg^{-1}. Group B received fentanyl every 20 min in log doses, in order to produce a linear increase of plasma concentrations to a point equivalent to the bolus of 100 μg kg^{-1}, at which time a further 100 μg kg^{-1} of fentanyl was administered.

In group A, fentanyl 100 μg kg^{-1} depressed the evoked cardiovascular response for 90 min, whereas in group B, fentanyl 100 μg kg, following pretreatment with fentanyl for 3 h, depressed $\Delta\overline{AP}$ and ΔHR only by 34% and 52% respectively at 5 min, compared with 79% and 84% in group A and for a shorter period (50 min for $\Delta\overline{AP}$ and 70 min for ΔHR.

Further evidence for tolerance in group B was observed, $\Delta\overline{AP}$ and ΔHR remaining unchanged during the pretreatment period with fentanyl 25, 39.8, 63 and 100 μg kg^{-1}, although the plasma concentrations increased progressively.

In conclusion, this study has shown that acute tolerance of the effects of fentanyl on somato–cardiovascular reflexes may occur within 2.5 h in the dog.

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RECOVERY FROM NEUROMUSCULAR BLOCKADE AFTER INFUSION OF ATRACURIUM

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Atracurium is a competitive neuromuscular blocking drug with a relatively short duration of action. Elimination of active drug is independent of hepatic, renal and circulatory function. Inactive metabolites are formed spontaneously at a rate which is determined by pH and temperature (Hofmann elimination) and by an enzymic ester hydrolysis which does not depend on pseudocholinesterase activity (Hughes and Chapple, 1981).

The effect of a complete paralysing dose of atracurium followed at intervals by increments of one-third or one-sixth of the initial dose has been reported (Payne and Hughes, 1981). We now report the results of administering atracurium by infusion following a small bolus dose.

The techniques used have been described elsewhere (Hughes, Ingram and Payne, 1976). The results of the present study are compared in table I with those obtained previously.

Five patients were given atracurium 0.1 mg kg^{-1} as a bolus, followed immediately by an infusion of 0.01 mg kg^{-1} min^{-1} for 30 min (a total dose of 0.4 mg kg^{-1}). The drug was diluted in physiological saline and infused by a calibrated syringe pump through a separate i.v. cannula. At the end of the infusion the height of the tetanic contraction had been reduced by a mean of 97.6% from its control value and an average time of 35.8 min was required for return to 95% of initial height. The rate constant for recovery was 9.2% per min.

These results are not significantly different from those obtained when atracurium was given in bolus doses of 0.3–0.9 mg kg^{-1}, but the time to 95% recovery was slightly shorter ($P < 0.05$) when it was administered as a bolus of 0.2 mg kg^{-1} and the rate constant for recovery from this dose was slightly faster ($P < 0.05$). This study provides further evidence of the lack of cumulative effects of atracurium at doses in the clinically useful range.

TABLE I. *Tetanic responses of the adductor pollicis muscle after neuromuscular block by atracurium (mean ±SEM).* *$P < 0.05$. †*0.1 mg kg^{-1} as a bolus followed by 0.01 mg kg^{-1} min^{-1} for 30 min.*

Dose (mg kg^{-1})	No. of patients	% Block	Time to 95% recovery (min)	Rate constant for recovery (% per min)
0.2	9	99.9±0.1	28.9±2.3*	12.0±1.0*
0.3	7	100	34.9±1.9	10.1±0.6
0.6	6	100	34.5±4.4	12.4±1.4
0.9	5	100	42.2±3.6	9.4±1.2
0.4†	5	97.6±0.9	35.8±1.7	9.2±0.7

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PHARMACOKINETICS OF PANCURONIUM BROMIDE IN LIVER FAILURE

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In the Liver Unit at King's College Hospital, patients in Grade IV hepatic coma often require ventilation. Pancuronium bromide is the neuromuscular blocking agent commonly used to paralyse these patients. Its pharmacokinetic profile has been described in patients with obstructive hepatic disease (Somogyi, Shanks and Triggs, 1977) and in cirrhosis (Duvaldestin et al., 1978) but not in acute hepatic failure. We have investigated the pharmacokinetic profile of pancuronium in a small group of patients with fulminant liver failure (group I) and compared it with that for patients (group II) without liver disease. All the patients studied had satisfactory renal function.

A predetermined dose of pancuronium was injected at time zero and serial blood samples taken at fixed points. Plasma was extracted within 1 h from each sample and stored at −20°C. Sampling in the liver group was from an arteriovenous fistula and in the control group from a central vein.

The concentration of pancuronium in each sample was measured fluorimetrically using the modified Rose Bengal method described by Wingard and others (1979). Plasma decay curves were plotted and pharmacokinetic parameters for the two groups calculated. For comparative analysis all data were fitted to a two-compartment model (table I).

TABLE I. *Calculations for redistribution and elimination half-lives, plasma clearance and apparent volumes of distribution. (Mean ± SD.) Statistical comparison by Student's* t *test*

	Group II normal ($n = 5$)	Group I liver ($n = 5$)	P
$T_{\frac{1}{2}}^{\alpha}$ (min)	3.07 ± 1.5	2.46 ± 1.22	n.s
$T_{\frac{1}{2}}^{\beta}$ (min)	93.94 ± 35.8	303.4 ± 196	< 0.05
Clearance (ml min^{-1} kg^{-1})	1.416 ± 0.273	0.565 ± 0.244	< 0.001
V_1 (ml)	4870 ± 1770	4820 ± 1560	n.s.
V_2 (ml)	8410 ± 2780	8500 ± 1850	n.s.

Significant differences were noted between the elimination half-lives and plasma clearances in the two groups. The volumes of distribution were remarkably similar.

It was noted that the liver failure group patients required "top up" doses of pancuronium at much greater plasma (compartment I) concentrations than in control patients. This, allied with the slow plasma clearance, may explain why patients with hepatocellular disease require higher initial doses of pancuronium with subsequent difficulty in antagonism of residual neuromuscular blockade.

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EVALUATION OF INFUSION RATES FOR NEW I.V. ANAESTHETIC AGENTS

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Continuous i.v. infusions of anaesthetic agents may be used to maintain anaesthesia. As this technique may be combined with the use of myoneural blocking drugs, it is necessary to ascertain the infusion rate required to maintain narcosis. We have studied the use of ICI 35 868 (di-isopropyl phenol in Cremophor), to determine an infusion rate which would anaesthetize all patients.

Following an induction dose of 2 mg kg^{-1} the drug was given by intermittent injection to 20 healthy unpremedicated patients in combination with 67% nitrous oxide in oxygen, for body surface operations lasting 45 min or longer. The individual maintenance requirements decreased within the range 50–180 μg kg^{-1} min^{-1} (mean, 100) showing a right skew distribution. By performing a $\log_e$ transformation a normal distribution was obtained.

For the main study, 70 unpremedicated patients were allocated randomly to one of seven groups receiving infusion rates of 33, 49, 65, 81, 97, 114 and 130 μg kg^{-1} min^{-}, with further supplements of ICI 35 868 as required. Patients breathed spontaneously 67% nitrous oxide in oxygen and the reaction to skin incision was monitored closely. There was an increase in the number of patients adequately anaesthetized with the infusion alone as the infusion dose was increased (fig. 1), and a dose of 200 μg kg^{-1} min^{-1} was necessary to ensure anaesthesia in all patients in this group.

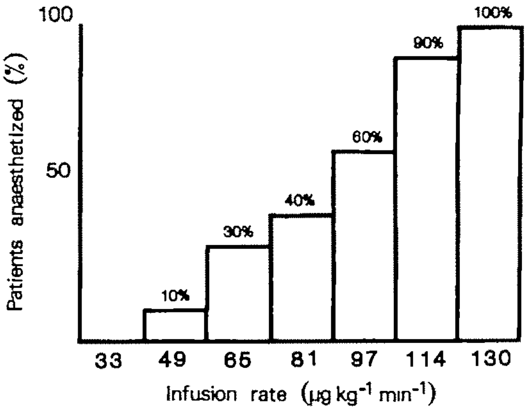

FIG. 1. Percentage of patients anaesthetized at different infusion rates.

The data showed that a median infusion rate plus increments produced greater total drug usage than a higher infusion rate which needed no supplements. Maintenance requirements were achieved by intermittent injection alone, or the correct infusion rate alone.

ACUTE DESENSITIZATION OF THE CENTRAL RESPIRATORY EFFECTS OF MIDAZOLAM IN THE DOG

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Midazolam hydrochloride, a relatively new water-soluble benzodiazepine, has been used to produce both sedation and anaesthesia (Conner et al., 1978). In the anaesthetized dog, midazolam 2 mg kg^{-1} has been shown to depress central respiratory activity up to 90 min (Whitwam et al., 1980). As benzodiazepines are believed to have specific central receptors (Squires and Braestrup, 1977), tolerance could develop to the effects of these drugs.

The present study was concerned with the effect of repeated i.v. doses of midazolam on central respiratory activity. Experiments were performed on eight dogs anaesthetized with methohexitone 10 mg kg^{-1} followed by α-chloralose 1–2 mg kg^{-1} h^{-1} and ventilated artificially via an endotracheal tube. Temperature and blood-gas tensions were maintained constant throughout each experiment. (The ranges between preparations were: temperature 37–38°C, Pa_{O_2} 24–29 kPa, Pa_{CO_2} 5.3–6 kPa and pH 7.32–7.46.) The e.c.g., beat-by-beat heart rate and mean arterial pressure were recorded. The phrenic nerve was exposed in the neck, desheathed, cut distally, immersed in mineral oil and its activity recorded using bipolar silver–silver electrodes.

When stability was obtained, a dose of midazolam 0.1–0.25 mg kg^{-1} was administered i.v., which reduced or abolished activity in the phrenic nerve. This activity returned subsequently to control values at 45–100 min. On return to control values the same dose was repeated four or more times.

After the first two doses, the degree and duration of central respiratory depression rapidly diminished in response to subsequent doses of midazolam.

To determine the nature of this acute desensitization, another "train" of four doses of midazolam was given after a period of 2 h, when it was shown that the preparation had recovered and a similar phenomenon re-occurred in a similar sequence.

It was concluded that the central respiratory effects of repeated doses of midazolam administered i.v. showed an acute desensitization which probably represents a form of tachyphylaxis.

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COMPARISON OF THE EFFECTS OF METHOHEXITONE AND KETAMINE ON SPINAL REFLEXES: EVIDENCE FOR TRANSMITTER RECEPTORS AS THEIR SITES OF ACTION

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Because of the different clinical spectra of ketamine and barbiturates such as methohexitone, we compared the effects of these two drugs on the physiology of the cat spinal neurones. Methohexitone 10 mg kg^{-1} i.v. was found to enhance GABA-mediated inhibitions but not glycine-mediated inhibitions, with concomitant small effects on monosynaptic (MS) and polysynaptic (PS) reflexes of decerebrate cats.

Ketamine 2.5–10 mg kg^{-1}, produced no consistent effect on inhibitions or on the MS reflex, but PS reflexes were reduced consistently with a recovery time similar to that of ketamine anaesthesia. These results suggest that ketamine reduces the release, or the postsynaptic effect, of an excitatory transmitter.

Using the technique of microelectrophoresis, (±) ketamine was found to depress selectivity responses to an L-aspartate analogue, N-methyl-aspartate (NMA) used to classify amino acid receptors mediating synaptic excitations in the c.n.s. (McLennan and Lodge, 1979). On 35 spinal neurones, responses to NMA were reduced more than those to quisqualate and kainate, substances used to classify two other receptor types. NMA-antagonism by ketamine was accompanied by reduction of the synaptic exciation of nine spinal neurones following stimulation of high-threshold afferents. Ketamine 2.5–10 mg kg^{-1} i.v. had similar effects on both amino acid and synaptic excitations.

Anaesthetic doses of ketamine thus exert a potent antagonistic action on excitatory amino acid receptors responsible for some of its central depressant effects. In contrast, methohexitone, in common with other barbiturates (Evans, 1979) acts largely via enhancement of GABA inhibitory actions.

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EFFECT OF HELIUM CONCENTRATION ON PEAK FLOW OF GASES

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The therapeutic benefit of inspired helium and oxygen mixtures on the work of breathing in patients with upper airway obstruction is well documented (Lu et al., 1976; Duncan, 1979). However, previous studies have relied on changes in arterial oxygen tension and airway pressures as indicators of improvement in ventilation. The present study was designed to quantify the effect of different concentrations of helium and varying concentrations of nitrogen in 21% oxygen on gas flow through a variable orifice.

A reservoir bag was ventilated by a modified Cape ventilator at a tidal volume of 500 ml and a frequency of 15 b.p.m. A variable constriction was placed between the bag and the inspiratory port of the ventilator. A pneumotachograph was used to measure the flow through the inspiratory limb of the system. The

TABLE I. *Percentage increase in peak flow through orifice, related to helium concentration.*

Peak flow rate (litre min^{-1})					
10		14		21	
Helium concn (%)	Flow increase (%)	Helium concn (%)	Flow increase (%)	Helium concn (%)	Flow increase (%)
10.0	12.6	11.6	8.5	9.8	1.4
23.0	24.7	19.5	20.9	19.5	15.9
30.0	36.8	30.9	28.6	30.0	17.1
40.6	46.8	40.6	37.2	40.1	19.7
49.8	50.6	51.0	38.8	50.6	22.9
64.1	60.4	61.0	44.8	57.7	24.4
68.9	65.4	71.3	48.2	73.1	24.5

concentrations of helium, oxygen and nitrogen were measured using a mass spectrometer. The outputs from these devices were interfaced with a microcomputer, which corrected the flow measurements, breath-by-breath for the composition of the gas mixture in the system.

The constriction was adjusted to produce peak flow rates, using air, of approximately 10, 15, and 20 litre min^{-1}. At each flow rate, the concentration of helium was increased incrementally to 70%, while the oxygen concentration was maintained at 21%. The flow measurements at each helium concentration were corrected for the minor variations which occurred when the system was used with the constriction removed.

The results (table I) show that the major part of the increase in peak flow occurred at concentrations up to 40% helium. Higher concentrations produced a modest improvement.

This information may help to rationalize the administration of 21% oxygen and 79% helium mixtures by face-mask to patients with upper airway obstruction.

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SERVO-CONTROL OF CLOSED CIRCUIT ANAESTHESIA

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A closed-circuit anaesthetic machine has been constructed as shown in figure 1. Liquid anaesthetic is injected into the circuit by a motor-driven syringe. Evaporation of anaesthetic and mixing within the circle are achieved with a Revel circulator (Morris, 1974), a small fan which drives gas round the circuit. The concentration of anaesthetic breathed by the patient is measured by the Engström Emma (Luff and White, 1981) anaesthetic gas meter. The sensor of the Emma is mounted in the deadspace between the circle and the patient. The end-tidal concentration is detected electronically and maintained at a pre-set value via a

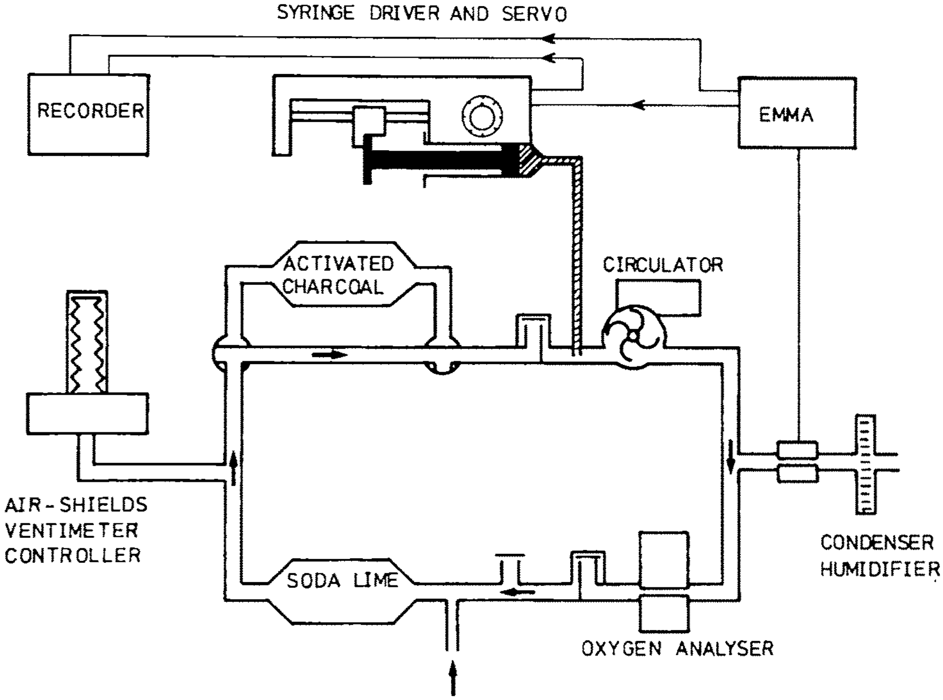

FIG. 1. Circuit used for servo-control of anaesthesia with a volatile agent.

feed-back loop. By integrating the output of a tachometer attached to the syringe driver, the amount of volatile agent injected is recorded

Data obtained in this way during clinical anaesthesia will be presented.

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MEASUREMENT OF THE INACCURACY OF OESOPHAGEAL PRESSURE FOR PLEURAL PRESSURE ESTIMATION

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Assessment of pleural pressure (and hence the elastic properties of the lung) usually depends on oesophageal pressure measurement. In supine anaesthetized subjects, pleural pressure may not be satisfactorily transmitted to the oesophageal lumen. This impairment of transmission may be assessed during an inspiratory attempt against a closed airway. In the dog, airway pressure and directly measured pleural pressure change almost identically during this manoeuvre (Morgan, Downs and Weled, 1980). If pleural pressure were fully transmitted to the oesophagus, oesophageal pressure should change similarly, and the differential pressure ($P_{aw} - P_{oes}$) should not alter.

Eight patients were studied in the supine position during varicose vein surgery. Halothane anaesthesia was administered by endotracheal tube, one-way valve, and T-piece. An oesophageal catheter was placed with the balloon (5 cm long ×0.5 cm diameter) immediately above the diaphragm. Simultaneous recordings were made of P_{aw} and ($P_{aw} - P_{oes}$) with the balloon in this position and at 5-cm intervals proximally in the oesophagus, during occlusion of inspiration. Recordings were taken also during progressive ventilatory stimulation by rebreathing and after occlusion of the preceding expiration so that the inspiratory attempt started at a lung volume of (FRC + V_T).

During the inspiratory attempts ($P_{aw} - P_{oes}$) usually decreased. This occurred for all measurement points in the oesophagus in seven of the patients. In two patients ($P_{aw} - P_{oes}$) did not change when the balloon was in the first position. The change in P_{oes} was proportional to the airway pressure change (0.74±0.15 SD) and was not influenced by ventilatory stimulation or by an inspiratory attempt at (FRC + V_T). The differences were greater than the nonhomogenous changes in alveolar pressure found in dogs (Brown, Scharf and Ingram, 1980).

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EFFECT OF ADDED VASOCONSTRICTORS ON SPINAL ANAESTHESIA WITH HYPERBARIC BUPIVACAINE

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For many years vasoconstrictors have been added to local anaesthetic solutions in an attempt to increase the duration of loss of sensation. However, in the case of spinal anaesthesia the doses recommended and the results reported vary widely. In a previous study (Chambers et al., 1981) we did not find any clinically useful prolongation of spinal anaesthesia using 5% lignocaine 1.5 ml in 7.5% dextrose with the addition of up to 0.3 ml of 1:1000 adrenaline.

Bupivacaine in hyperbaric solution has been investigated recently as an agent for spinal anaesthesia (Moore, 1980; Chambers, Edstrom and Scott, 1981) and has been shown to produce consistently good spinal nerve blockade. We have carried out the following study to assess the effects of added vasoconstrictors on intrathecal bupivacaine. Thirty patients who underwent transurethral resection of the prostate received intrathecally 0.5% bupivacaine 3 ml in 8% dextrose, either alone or in combination with either 1:1000 adrenaline 0.2 ml or 1% phenylephrine 0.5 ml. Patients remained awake throughout the procedure and assessments were made of the sensory and motor blockade at times up to 30 min after injection and at 15-min intervals thereafter until no sensory loss was demonstrable.

The addition of phenylephrine gave a small prolongation of the block which was not statistically significant (table I). Although added adrenaline produced a greater prolongation, this only reached statistical significance with regard to total duration. Three patients who had received solutions which contained a vasoconstrictor had very prolonged blocks, but these solutions could not be relied upon consistently to produce a clinically significant increase in duration in individual patients.

TABLE I. *Mean (+SEM) times (min) until no sensory loss was detectable and until motor block had recovered sufficiently for the patient to raise the extended leg, in the three groups of patients. *n = 9; one patient in this group was always able to raise his extended leg*

	Solution used		
	Plain solution	With phenylephrine	With adrenaline
Sensory	197±10.8	221±11.4	231±24.6
Motor	122±11.7	147±16.3	163±19.3*

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PLASMA CATECHOLAMINES IN ANAESTHESIA

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There has been considerable interest for some time in the measurement of plasma concentrations of catecholamines as a measure of the response to stress occuring in the perioperative period. This was facilitated in 1976 by the development of a radioenzymatic technique (Cryer, 1976) which is highly sensitive, but unfortunately this method is time-consuming, tedious and relatively expensive.

Recently, techniques have been described for measurement of catecholamines using high performance liquid chromatography (HPLC) (Hallman et al., 1978; Hjemdahl, Daleskog and Kahan, 1979). The present report describes the modification of these methods for use in our laboratory and also presents some preliminary results from concurrent studies of various postoperative analgesic regimes.

In this technique, after initial purification with aluminium oxide, the catecholamines were separated by cation exchange chromatography using a precolumn and electrochemical detection at a potential of 0.52 V.

Values obtained in our laboratory for plasma catecholamine concentrations in volunteers are similar to measurements obtained elsewhere by radio enzymatic assay. Mean values in venous blood of resting subjects were 0.26±0.12 pmol ml^{-1} (mean±1 SD, $n = 11$) for adrenaline and 1.18±0.6 pmol ml^{-1} for noradrenaline. In 64 unpremedicated patients awaiting either upper or lower abdominal surgery, mean plasma concentrations were 0.3±0.2 pmol ml^{-1} for adrenaline and 2.2±1.3 for noradrenaline. Twenty-four hours after operation there was a highly significant increase to values of 0.3±0.2 and 3.7±1.9 respectively, obtained during a period of relative comfort induced by analgesic drugs.

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COMPARISON OF HALOTHANE AND FENTANYL SUPPLEMENTATION TO GENERAL ANAESTHESIA ON THE STRESS RESPONSE OF PATIENTS UNDERGOING UPPER ABDOMINAL SURGERY

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Major surgery increases sympathetic nervous system activity, which is reflected by changes in circulating catecholamine concentrations. We have compared the stress responses of patients after addition of an analgesic, fentanyl, with those receiving halothane supplementation (Hall, 1980).

TABLE I. *Effect of halothane and fentanyl 10 μg/kg body weight supplementation to general anaesthesia during upper abdominal surgery on plasma concentrations of noradrenaline, cortisol and glucose (mean ± SD). Significant difference compared with values before induction:* *$P < 0.05$, **$P < 0.005$, ***$P < 0.001$, ****$P < 0.0001$ *(analysis of variance)*

	Group	Before induction	15 min after induction	Maximum stimulation	15 min after recovery
Noradrenaline	Halothane	4.8±2.7	7.2±4.4	13.2±10.7***	11.4±10**
(nmol litre^{-1})	Fentanyl	2.9±1.2	2.6±2.4	5.6±2.2	9.7±6.9
Cortisol	Halothane	365±125	485±222	816±176*	959±145****
(nmol litre^{-1})	Fentanyl	435±187	490±254	755±237*	990±244***
Glucose	Halothane	4.8±0.3	5.3±0.5	7.2±1.0***	7.7±1.3****
(mmol litre^{-1})	Fentanyl	4.6±0.5	4.5±0.6	5.9±0.9*	6.7±1.5**

Twenty patients, aged 18–65 yr, undergoing elective upper abdominal surgery (vagotomy and pyloroplasty or cholecystectomy) gave informed consent to participate in this study. Patients with a history of excessive alcohol consumption or of intake of drugs affecting autonomic function were excluded. Premedication comprised lorazepam 2 mg orally 90 min before induction of anaesthesia with thiopentone 5 mg kg^{-1} i.v. Muscle relaxation was produced using pancuronium 0.1 mg kg^{-1} and an endotracheal tube was inserted. Ventilation was controlled and anaesthesia maintained with a mixture of 66% nitrous oxide in oxygen. In 10 patients anaesthesia was supplemented with 0.5–1.5% halothane, while the other 10 patients received supplementation with fentanyl in a dose of 10 μg kg^{-1} i.v. initially and increments of 2.5 μg kg^{-1} as required. Blood was collected before induction, 15 min after induction but before surgery, at the time of maximal stimulation during surgery (soon after vagotomy or cholecystectomy), and 15 min after the patient had recovered sufficiently to respond to spoken commands. Plasma noradrenaline concentration was measured by a sensitive radio-enzymatic method (Henry et al., 1975). Plasma glucose and cortisol were measured by conventional techniques.

Plasma noradrenaline concentration increased significantly ($P < 0.001$) during maximal stimulation and remained increased on recovery in the patients receiving halothane, but did not increase significantly with fentanyl (table I). Plasma glucose increased more in response to halothane than with fentanyl, but there was little difference in the changes in plasma cortisol between the groups.

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THE ROLE OF CREMOPHOR EL IN ANAPHYLACTOID REACTIONS TO I.V. ANAESTHETICS

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Desirable pharmacokinetic properties and freedom from excitatory effects may be more readily obtained with highly lipophilic, rather than with water soluble anaesthetic compounds. Problems in solubilizing lipophilic compounds remain, as doubt exists about the involvement of the solubilizing agent, Cremophor EL, in anaphylactoid reactions. Lorenz (1975) has speculated that the role of Cremophor in producing reactions in man may be related to the combined effects of a surfactant with an anaesthetic agent, the mast cell membrane being altered by the anaesthetic drug to facilitate binding of the wetting agent and release of histamine. We have found that surfactants differ in their ability to produce histamine release on first administration to dogs. Cremophor EL and Tween 80, when given by i.v. injection, are potent liberators of histamine in this species, whereas Synperonic PE 39/70, a synthetic polyoxypropylene-polyoxyethylene block co-polymer, is much less likely to produce histamine release.

The miniature pig is a sensitive model for reactions to Cremophor-containing anaesthetics (Glen, et al., 1979). We have examined the effects of i.v. injection of 10% or 20% aqueous solutions of Cremophor, Tween and Synperonic in the pig. On a first administration, none of the materials produced any adverse response. When a second injection of surfactant, at a dose of 25–50 mg kg^{-1}, was given 7 days after the first administration, the animals given Cremophor and Tween showed typical anaphylactoid responses. No responses were seen in pigs given a second injection of Synperonic PE 39/70. Although histamine release in the dog may be of little predictive value in relation to histamine release in man, the present results suggest that the physical property of a surfactant which produces mast cell degranulation in the dog may also be important in sensitizing "memory cells" to a second administration of the compound in the pig, and possibly in man.

The new i.v. anaesthetic disoprofol (Diprivan, ICI 35 868) can be solubilized with Synperonic PE 39/70 and in this formulation failed to produce any anaphylactoid response in the pig model. Problems in obtaining a consistent chemical specification for Synperonic have prevented the clinical development of this particular formulation. However, this study has demonstrated that the combination of a surfactant with an anaesthetic does not always induce reactions and that the properties of the surfactant are probably of major importance. This suggests that a suitable non-Cremophor formulation of disoprofol should be less likely to produce the "short-term memory" type of anaphylactoid response which may be associated with Cremophor-containing agents.

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POSTER DEMONSTRATIONS

VENOUS SEQUELAE FOLLOWING I.V. ANAESTHETICS AND BENZODIAZEPINES

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Thrombosis or thrombophlebitis is a not infrequent complication of i.v. anaesthesia, particularly with non-aqueous solutions, although published estimates of the occurrence vary widely. Hegarty and Dundee (1977) found a greater frequency of sequelae on the 7th–10th days after i.v. Valium (0.5% diazepam in organic solvents) than on the 2nd–3rd days. As most workers have based their findings either on early observations or on a questionnaire (Schou Olesen and Huttel, 1980), we have carried out a long term (7–10 day) follow-up of the effect of commonly used i.v. anaesthetics.

The test drug was injected directly to a clearly defined vein with the precautions described by O'Donnell, Hewitt and Dundee (1969). Follow-up was on the 2nd–3rd and 7th–10th days. The drugs studied were 2.5% thiopentone, 1% methohexitone and 1% ICI 35 868 (di-isopropyl phenol in 16% Cremophor), two forms of diazepam — Valium and Diazemuls — (soya bean oil solvent) and the water-soluble benzodiazepine, 0.5% midazolam. In addition, 50 subjects received i.v. saline 0.9%.

There was an unacceptably great frequency of sequelae (mostly thrombosis) after Valium, but no long-term effects with Diazemuls. In contrast, midazolam caused few complications. The frequency was unexpectedly great with methohexitone and similar to that with ICI 35 868 (table I).

Table I. *Percentage frequency of all types of sequelae following i.v. administration of drugs.*

	Saline	Thio-pentone	Metho-hexitone	ICI 35 868	Valium	Diazemuls	Midazolam
No. of patients	50	50	50	50	50	50	100
Days: 2–3	2	4	10	8	22	2	2
7–10	0	0	10	2	36	0	6
Total	2	4	10	10	40	2	8

Neither the size nor the site of the vein influenced the frequency of thrombosis, although the administration of both Valium and ICI 35 868 to small veins was too painful for routine use. Because of the relationship of pain on injection to vein size, it was not possible to relate independently pain and the recurrence of thrombosis.

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MICROPROCESSOR-BASED ANALYSIS OF SKELETAL MUSCLE TWITCH TENSION

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A variety of tests dependent basically on passive tension or contracture response from *in vitro* skeletal muscle biopsies have been developed successfully to screen for susceptibility to malignant hyperthermia. Active twitch tension responses have been used fundamentally to test for viability of preparations (Ellis et al., 1972) or to standardize them at the optimum length (Leslie and MacLachlan, 1976), but otherwise have been little studied *per se* as a possible adjunct or alternative to present screening procedures. This may be a consequence of the time and effort necessary to perform the painstaking detailed analysis of many tens or hundreds of muscle twitches. Recently we have developed microprocessor software that analyses "on-line" *in vivo* twitch tensions of motor units from rat soleus challenged i.v. with dantrolene sodium (Leslie and Part, in preparation) and have adapted the software to analyse tape-recorded responses from *in vitro* muscle biopsy preparations. This latter aspect is the subject of the present report.

The system's hardware is centred on an MZ-80K (Sharp) microprocessor with custom-built A/D converter interface (3D Ltd, London), capable with machine code programming of maximal sampling at 20 kHz. The software is worked in BASIC and permits control of tape recorder, the gathering, A/D conversion and memory storage of individual muscle twitches and, further, the BASIC programmes provide presently for determinations of passive and peak twitch tensions, contraction and half-relaxation times, and maximum rates of increase and decrease of active tension. These data may be presented visually on the VDU, output to the printer (Microline 80) and stored on cassette tape for further, statistical, analysis. A number of software routines has been developed to display length–tension responses of such biopsies, also the effects of caffeine and halothane on their twitch parameters both in terms of absolute values and percentage normalized responses, together with data on potentiation effects. These various aspects will be demonstrated to the Society.

Our experiments have shown that such a dedicated microprocessor system (costing about £2500) can be used to assess objectively and display quantitatively muscle tension responses and their reactions to a variety of drugs. The analyses of tape-recorder responses are not yet statistically advanced enough to state if any aspect of twitch tension may be a desirable adjunct to malligant hyperthermia screening.

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ACCURACY OF THE OSCILLOTONOMETER

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Although Von Recklinghausen's modification of Gallavardin's oscillotonometer has been used widely in clinical practice, we have been unable to trace any detailed publication on the accuracy of the instrument. The performance of the Scala Alternans Altera oscillotonometer has been analysed and values of systolic, mean and diastolic arterial pressures were compared simultaneously with pressures measured directly from a brachial or radial artery in the same arm. Measurements were made in 11 patients undergoing arterial or middle-ear surgery, providing a range of systolic arterial pressures from 50 to 210 mm Hg, and of diastolic pressures from 30 to 110 mm Hg. Direct arterial pressures were recorded from a Hewlett–Packard 78205 pressure module with a Gould–Statham P23Ia transducer. The system had an amplitude–frequency response flat (±5%) to 30 Hz when dioxide measured and then morphine 2 mg in normal saline 10 ml was given via the extradural cannula. Patients were subsequently nursed supine (11 patients) or semi-sitting (10 patients). connected to the patient by Vygon manometer tubing (120 cm) and an 18-gauge Teflon cannula.

TABLE I. *Regression equations between oscillotonometer values of arterial pressure* (y) *and direct arterial pressure* (x). **Plotted together because there is no significant difference between the regressions of the different deflation rates*

Pressure detected	Speed of cuff deflation	Regression line	Correl. coeff. (no. of points)	95% Confidence bands
Systolic	Slow	$y=-3.7+0.98x$	$r=0.99$ $n=92$	±13.7 mm Hg
	Medium	$y=-3.9+0.93x$	$r=0.95$ $n=132$	±21.3 mm Hg
	Fast	$y=-1.0+0.81x$	$r=0.92$ $n=106$	±27.8 mm Hg
Mean	Slow + medium*	$y=2.4+0.97x$	$r=0.96$ $n=127$	±17.3 mm Hg
	Fast	$y=7.4+0.84x$	$r=0.95$ $n=56$	±16.5 mm Hg
Diastolic	Slow, medium + fast*	$y=6.4+0.83x$	$r=0.64$ $n=220$	±38.1 mm Hg

The oscillotonometers (accurately calibrated both statically and dynamically) were modified by replacing the variable leak with one of three fixed-orifice nozzles allowing cuff deflation from 200 mm Hg to 100 mm Hg over 5 s (fast), 17.5 s (medium) or 52 s (slow). The first "swing" of the oscillotonometer needle was correlated with direct systolic arterial pressure, the maximum amplitude of needle deflection was correlated with mean arterial pressure, and the point at which the needle swing changed to a small amplitude flick was correlated with diastolic arterial pressure.

The best correlation with direct systolic arterial pressure was obtained at the slowest rate of cuff deflation (table I). At faster deflation rates, the oscillotonometer consistently gave values below the true value, with wide confidence limits. The 95% confidence limits were so wide as to render the oscillotonometer useless for clinical measurement of diastolic pressures. The mean arterial pressure derived from the direct measurement correlated well with the maximum amplitude of the oscillotonometer needle swing at slow and medium deflation rates. The knurled leak valve of the oscillotonometer required to be released through an angle of only 30° in order to change from the slow to the fast deflation rate.

The mechanism of the oscillotonometer was investigated, and it was found that although the criterion for detection of systolic pressure corresponded well with phase differences in the pressure waves from the upper and lower cuffs, no similar end-point could be found for diastolic pressure. A wide range of resonant frequencies was found in 11 oscillotonometers tested, and of the exciting frequencies measured in 29 adults. The magnitude of the oscillotonometer needle swing depends on a specific interaction between the resonant frequency of the oscillotonometer and the characteristics of the patient's arterial system which determine the pulse-wave velocity.

COMPLEMENT AND CARDIOPULMONARY BYPASS

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During cardiopulmonary bypass, complement is known to be activated, releasing complement fragments C$_3$a and C$_5$a (Chenoweth et al., 1981), which are both anaphylotoxins. In addition C$_5$a causes aggregation of granulocytes and sequestration of C$_5$a-activated granulocytes in the lungs (Hammerschmidt et al., 1981). These anaphylotoxins and the sequestrated granulocytes may contribute to the pulmonary dysfunction which sometimes follows cardiopulmonary bypass and to the pathogenesis of the post-pump syndromes.

For this reason we have studied 10 patients undergoing elective coronary artery bypass surgery. Anaesthesia and cardiopulmonary bypass techniques were uniform and the duration of extracorporeal perfusion varied from 70 to 90 min (mean ±SD: 82±7.4 min). Total haemolytic complement (CH$_{50}$), C$_4$, C$_3$ and the alternative pathway activity were measured before operation, during and for 48 h after cardiopulmonary bypass.

TABLE I. *Complement assays. †Mean ± SD results expressed in % of standard pool of normal human serum. Significant difference: (by paired* t *test)* *$P < 0.01$; **$P < 0.001$; ***$P < 0.001$

	Before CPB		CPB		After CPB			
	24 h before op.	After heparin	10 min	60 min	After protamine	8 h	24 h	48 h
CH$_{50}$	80±10	61±13	62±22	64.1±21	71±11*	57±13**	53±13***	66±28
C$_3$	136±115	126±17	103±33*	107±21***	102±17***	99±19***	106±24**	131±57
C$_4$	141±54	137±67	139±103	111±48***	101±39***	96±35***	84±34***	114±56
Haemolytic alternate pathway	85±17	90±26	93±41	108±45	111±45	78±24	77.8±21	85±37

A significant reduction of CH$_{50}$ was seen after heparinization but before CPB. C$_3$ and C$_4$ showed no significant change in the period before bypass. We confirmed the reduction of CH$_{50}$, and the significant reduction of C$_3$ (table I) and the neutropaenia which occur during CPB and have been demonstrated in previous studies (Hammerschmidt et al., 1981). In addition a significant reduction of C$_4$ was observed (table I). There was no significant change in alternative pathway function and no C$_3$d was detected before, during or after bypass.

In the period after CPB we found that the reduction in CH$_{50}$ continued and became significant and C$_3$ and C$_4$ remained low. Although these were significantly reduced even 24 h later, the patients remained clinically well.

It was concluded that changes in complement concentration during CPB were not associated with evidence of complement activation, but are caused by some other mechanism.

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POSTOPERATIVE RESPIRATORY DEPRESSION ASSOCIATED WITH CONTINUOUS MORPHINE INFUSION

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We have shown that respiratory depression in the period after operation is manifest not only as hypoventilation, with impaired arterial blood-gas tensions, but also as transient disturbances of ventilation including apnoeic episodes (Catling et al., 1980). The patients in that study received papaveretum for pain relief following cholecystectomy. We embarked on the current study in order to establish whether these disturbances are caused by the use of opiate drugs or whether they result primarily from other causes such as upper abdominal surgery, general anaesthesia or sleep.

TABLE I. *Respiratory disturbances in the infusion (seven patients) and block (five patients) groups. Total number of observations in parentheses*

	Infusion group	Extradural/intercostal block group
Apnoea	6/7 (109)	1/5 (1)
Low oxygen saturation	4/7 (69)	0/5 (0)
Slow respiratory rate	3/7 (55)	1/5 (22)
Small tidal volumes	3/7 (14)	0/5 (0)
Mean pain scores, over 6 h (out of 100)	34	18

Patients who had undergone cholecystectomy or total hip replacement under standard general anaesthesia were allocated to two groups. Within 1 h after surgery one group received a loading dose of morphine sufficient to relieve pain and this dose was repeated as an infusion over 24 h. The other group received either an intercostal or an extradural nerve block using bupivacaine. All patients were monitored continuously during the first 16 h after surgery using respiratory inductance plethysmography, ear oximetry, electroencephalography and electrooculography. Pain scores also were recorded at regular intervals. Respiratory recordings were examined for periods of apnoea (longer than 15 s), low oxygen saturations (less than 80% persisting for longer than 5 s), slow respiratory rate (less than 8 beat min^{-1} persisting for 5 min) and small tidal volumes (less than 300 ml persisting for 5 min). These abnormalities were related to the patient's sleep state. Analysis of these data for the 12 patients studied is shown in table I.

The preliminary results showed that the patients who received an infusion of morphine had frequent signs of respiratory depression, in contrast to the patients who received regional nerve block. On completion of the study we hope to establish the way in which operation, analgesia and sleep state interact to cause respiratory depression in the period after surgery.

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COMPARATIVE PHARMACOKINETICS OF FENTANYL AND ALFENTANIL

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The pharmacokinetic characteristics of alfentanil were compared with those of fentanyl in seven healthy volunteers. Each subject was given 170 μg of each drug simultaneously as a 2.5-min i.v. infusion. Venous blood samples were taken over the period 0–360 min and the plasma separated and stored at −20 °C until assay. Each sample was assayed in triplicate for fentanyl and alfentanil content, by independent radioimmunoassays. The molar ratio of cross-reactivity of each drug in assay for the other was less than 10^{-4} in both cases.

Weighted, least squares, non-linear regression analysis was used to fit a biexponential curve to each set of data, and the corresponding two-compartment open model was derived. Total clearance of each drug was calculated as the product $V_1\,k_{10}$.

At least 3 weeks later, two of the subjects were given 1 mg of alfentanil alone, and the analytical procedure was repeated as before. The results are summarized in table I.

TABLE I. *Pharmacokinetics of fentanyl and alfentanil*

	Dose (μg)	*n*	$T_{\frac{1}{2}}^{\beta}$ (min)	V^{ss} (litre)	*Cl* (litre h^{-1});
Fentanyl	170	7	3.47	350.3	82.3
Alfentanil	170	7	1.63	26.9	14.0
	1000	2	1.42	26.1	14.9

The characteristics of fentanyl binding to plasma proteins of 15 healthy volunteers have been reported (Bower, 1981). The binding of alfentanil was studied in the same subjects by the same technique of equilibrium dialysis. Fentanyl bound 79.16% ± 1.07 (SD) up to a concentration of 500 μg ml^{-1}, while alfentanil bound 88.65% ± 1.68 up to 0.1 μg ml^{-1}.

Partition of both drugs between red blood cells and plasma was studied in 15 (fentanyl) and five (alfentanil) of the normal subjects. The red cell–plasma partition coefficient of fentanyl was 1.0, and that of alfentanil was 0.1.

The pharmacokinetic characteristics of the two drugs are consistent with the difference in their lipid solubility. Total clearance of alfentanil is approximately one-sixth that of fentanyl, and may reflect a lower hepatic extraction ratio from whole blood. Therefore entero-hepatic recirculation may cause a significant increase in the concentration of alfentanil in the plasma of the systemic circulation.

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PHARMACOKINETIC DATA OF FENTANYL, MIDAZOLAM AND ENFLURANE OBTAINED BY A NEW METHOD FOR ARBITRARY APPLICATION SCHEMES

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The determination of pharmacokinetic models is essential for a rational anaesthetic drug dose regimen. The transfer constants, which describe the distribution and re-distribution of drug between various compartments, are the model-defining constants in the framework of linear pharmacokinetics. In general these constants are estimated from plasma concentrations after a single bolus injection.

We developed a method for the determination of pharmacokinetic hybrid constants, and thus of transfer constants, from values obtained by arbitrary application schemes. In essence the method relies on a combination of the superposition principle of linear pharmacokinetics and a directed trial-and-error procedure for estimating model constants.

Some advantages are associated with this method:
One is not restricted to a single bolus for estimating transfer constants; aribitrary application schemes may be used. Thus the model constants can be obtained under more realistic conditions.
The model constants can be estimated more reliably. Using infusion techniques or repetitive dosing, plasma concentrations can be held at a range suitable for chemical detection methods for a longer period than with a single bolus. This is especially important for drugs with a short half-life.
The information from which mean values of pharmacokinetic data are estimated can be easily enlarged because one is not restricted to a certain application scheme.
One can obtain pharmacokinetic data for drugs not suited for bolus administration (e.g. volatile anaesthetics).

We report the application and results of this method for several application schemes (different infusion techniques and repetitive dosing) for fentanyl ($n = 20$) and midazolam ($n = 8$).

For enflurane ($n = 10$) we used mass spectrometer analysis of inspiratory and expiratory concentrations.

DISPOSITION OF ALFENTANIL, A NEW ANALGESIC AGENT, IN MAN

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Alfentanil (R 39209), a potent and very short acting morphine-like analgesic, was administered i.v. to five healthy female surgical patients in a dose of 120 μg kg^{-1} during halothane anaesthesia. We examined the alfentanil disposition in man to determine if its pharmacokinetic profile suggested potential advantages over currently available analgesics.

Plasma alfentanil concentration was determined by gas–liquid chromatography with specific thermionic detection. Plasma concentrations were fitted to a three-compartment open pharmacokinetic model.

Following i.v. injection, alfentanil concentrations decreased rapidly and 96.4% of the dose was eliminated from plasma in 60 min. The disappearance of the drug from plasma occurred quickly: mean values ($\pm$SD) were 3.5 ± 1.3 min for the initial $T_{\frac{1}{2}}$, 16.8 ± 6.4 min for the intermediate $T_{\frac{1}{2}}$ and 94 ± 38 min for the apparent elimination half-life.

The volume of the central compartment was estimated at 12 ± 2.3 litre; the total apparent volume of distribution reached 1.03 ± 0.5 litre kg^{-1}, indicating less tissue accumulation than with other analgesics.

Total plasma clearance was estimated as 456 ± 155 ml min^{-1}. As the rate constant k_{31}, representing return of alfentanil from the peripheral to the central compartment, was less than the elimination rate constant k_{10}, the re-uptake into plasma from remote peripheral tissues could be the rate-limiting step in the elimination of alfentanil.

The short duration of the pharmacological effect might be explained by the rapid redistribution of the drug from the intermediate to the remote peripheral compartment ($k_{21} > k_{13}$).

EFFECT OF INTRATHECAL MORPHINE ON THE ELECTROPHYSIOLOGICAL ACTIVITY OF THE URETER IN RABBIT

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Morphine has been known to increase the peristaltic activity of the ureter. Lately, extradural morphine has been introduced in the treatment of ureterocolic because it provides prolonged analgesia and we wished to know if this method might facilitate elimination of a stone.

In the present electrophysiological study, the ureter was exposed in anaesthetized rabbits and a coaxial needle was inserted to the muscle. The recordings were amplified ×5000, recorded on a 0–5000 Hz FM recorder and computer-processed. The electrophysiological activity was recorded continuously before and after the intrathecal injection of morphine 2 mg.

The ureteral muscle has a spontaneous slow non-rhythmic activity, with a duration of 1.0–1.5 s, frequency of 1–2 contractions per 10 s and amplitude of 0.3–0.7 mV. Bursts of phasic (fast) activity were apparent, sometimes superimposed and sometimes between the waves of slow activity.

All the indices of the slow and fast electrophysiological activity were increased by intrathecal morphine. I.v. administration of naloxone 0.4 mg counteracted the effects of morphine.

We conclude that direct electrophysiological studies of the ureteral muscle are feasible in animals and constitute a reliable means of measurement of the effect of various drugs on the ureteral activity. Intrathecal morphine increases slow and fast contractions.

SPINAL BLOCK WITH LIGNOCAINE AND FENTANYL FOR ENDER NAILING IN THE ELDERLY

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The combination of fentanyl with a local anaesthetic for spinal block has been advocated by De Castro and others (1980) in order to improve analgesia with less risks than those carried by intrathecal morphine. This study was undertaken to investigate a combination of 5% hyperbaric lignocaine with fentanyl and to answer two questions: does adding fentanyl 50 μg to lignocaine 100 mg improve analgesia? Does intrathecal fentanyl provide better analgesia than i.m. fentanyl? The study was double-blind in 50 patients more than 65 years old, with fractured neck of femur and undergoing Ender nailing. The patients were randomly allocated to receive one of three combinations (table I).

We compared onset time, concentration, intensity and duration of analgesia, also effects on breathing and circulation. No significant differences were found between the three groups and anaesthesia was quite satisfactory whatever the solution. The similar behaviour of the groups is probably related to the patients'

TABLE I. *The analgesic regimen*

	Intrathecal route	Intramuscular route
Group I ($n = 17$) (no fentanyl)	Lignocaine 5% 2 ml; adrenaline 1:1000 0.1 ml; dist. water 1 ml (= placebo).	Normal saline sol. 1 ml (= placebo)
Group II ($n = 16$) (i.m. fentanyl)	Lignocaine 5% 2 ml; adrenaline 1:1000 0.1 ml; dist. water 1 ml	Fentanyl 1 ml (50 μg)
Group III ($n = 17$) (intrathecal fentanyl)	Lignocaine 5% 2 ml; adrenaline 1:1000 0.1 ml; fentanyl 1 ml	Normal saline sol. 1 ml

poor mental status which hinders enquiry about analgesia. We conclude that concomitant use of fentanyl is not of benefit in old patients operated on by means of a spinal block for Ender nailing.

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EXTRADURAL MORPHINE IN OBSTETRIC ANAESTHESIA

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Women between 19 and 36 years of age who were undergoing labour and delivery were treated with extradural morphine either after a Caesarean section, for postoperative pain relief, or for vaginal delivery.

The analgesic effects, the plasma morphine concentration and possible side-effects were examined at intervals and immediately after birth.

The analgesic effects of morphine 5 mg during labour and delivery were inadequate when compared with either bupivacaine or chloroprocaine anaesthesia. The analgesic effects of extradural morphine for postoperative pain relief were as good as for the obstetric procedure.

The onset of analgesia varied from 5 to 20 min and the analgesic effect lasted between 24 and 48 h.

The postpartum maternal plasma concentration of morphine ranged around 0.08 $\mu g\ ml^{-1}$ 1 h after the administration and had decreased to 0.04 $\mu g\ ml^{-1}$ after 4 h. The values were negligible 12 h following extradural morphine.

The maternal and neonatal plasma morphine concentrations seemed to depend on the induction–delivery interval. If the interval was 15 min and morphine 5 mg was given, the maternal and neonatal plasma concentrations ranged around 0.03 $\mu g\ ml^{1}$. These values were only slightly greater 60, 120 and 180 min later. If morphine 10 mg was administered instead of 5 mg, the variation of maternal and neonatal plasma concentrations was about 50% greater.

Minor side-effects such as drowsiness and nausea were rare with the 5 mg dose, whereas 10 mg caused nausea and vomiting, as well as itching, in about 50% of the patients.

VENTILATORY EFFECTS OF EXTRADURAL DIAMORPHINE

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Late and severe ventilatory depression has been reported as a complication of morphine or other opiates injected intrathecally or in the extradural space (Glynn et al., 1979; Scott and McClure, 1979). To evaluate the ventilatory effects of extradural opiate analgesia we have compared the effects of diamorphine with those of lignocaine injected through an extradural catheter placed in the mid-thoracic region.

Fourteen patients were studied on the day before surgery, and on the 1st day after dacron prosthetic replacement of the lower aorta. During surgery, and for the night following surgery, segmental extradural analgesia was provided with 0.375% bupivacaine. On the morning of the 1st day after operation, measurements of ventilation, ventilatory mechanics, arterial blood gases (table I) and ventilatory response to carbon dioxide were performed: stage B = when the effects of previous extradural analgesia had ceased; stage C = during the peak effect of segmental analgesia (T4–T12) induced with 1.5% lignocaine; stages D, E, F, G = 30 min, 2, 4 and 6 h after establishment of extradural analgesia with diamorphine 5 mg in saline 10 ml.

These observations were compared with measurements obtained in the awake patient on the day before surgery (stage A).

Both lignocaine and diamorphine provided effective analgesia in the period after operation, which significantly improved the patient's forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) measurements without causing severe impairment of ventilation. Relief of pain was confirmed by the patient's assessment recorded on a visual linear analogue scale.

Pa_{CO_2} values 30 min after diamorphine were significantly greater than preoperative values (stage A), or at stages D and F, but the greatest individual Pa_{CO_2} was only 6.30 kPa.

Measurements of the ventilatory response to carbon dioxide confirmed that extradural diamorphine did not cause severe ventilatory depression. No evidence of late ventilatory depression was observed in this series of patients.

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Table I. *Ventilatory and circulatory responses to extradural lignocaine or diamorphine. Significance of results compared with stage B.* * $2P < 0.05$

Stage	Mean arterial pressure (mm Hg)	$\dot{V}_E$ (litre min^{-1})	f (b.p.m.)	FVC (litre)	FEV_1 (litre)	Pa_{CO_2} (kPa)
A	104 ± 7	10.2 ± 2.9	15.4 ± 4.7	3.30 ± 0.90	2.30 ± 0.80	4.85 ± 0.49
B	101 ± 15	10.0 ± 2.5	20.9 ± 6.9	1.22 ± 0.52	0.88 ± 0.39	4.92 ± 0.39
C	65 ± 9*	9.6 ± 1.8	20.5 ± 5.9	1.54 ± 0.64*	1.12 ± 0.50	4.81 ± 0.35
D	91 ± 16*	7.8 ± 1.5*	15.8 ± 5.2*	1.63 ± 0.49*	1.20 ± 0.46*	5.20 ± 0.43*
E	92 ± 16	8.5 ± 1.5*	17.9 ± 5.7	1.59 ± 0.49*	1.09 ± 0.43	5.15 ± 0.52
F	92 ± 17	9.2 ± 1.9	19.8 ± 5.4	1.55 ± 0.56*	1.07 ± 0.49*	5.19 ± 0.40*
G	91 ± 19	10.1 ± 2.1	19.3 ± 4.7	1.53 ± 0.62	1.11 ± 0.62	5.01 ± 0.47

EFFECTS OF EXTRADURAL ANALGESIA WITH ETIDOCAINE AND OPIOIDS ON ENDOCRINE FUNCTION

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The pituitary–adrenocortical response to surgical stress was studied in 56 patients, 56–75 years old, undergoing extradural analgesia using etidocaine and buprenorphine or fentanyl. The patients were divided into four groups according to operation and the opioid: groups I and III comprised patients undergoing total hip arthroplasty and groups II and IV patients undergoing inguinal hernioplasty. In groups I and II extradural block was performed using 1% etidocaine 150–200 mg plus buprenorphine 0.3 mg; groups III and IV received extradural analgesia with 1% etidocaine 150–200 mg plus fentanyl 0.15 mg. Analgesia extended from T4–6 to S5. All patients were premedicated with diazepam 10 mg and atropine 0.5 mg. Flunitrazepam was used to supplement analgesia. All patients received sodium chloride 0.15 mol litre^{-1} 20–25 ml kg^{-1}. Blood samples were drawn for measurements of growth hormone (GH), prolactin, ACTH, cortisol, aldosterone (PA), renin activity (PRA) and insulin. The samples were obtained 10 min before induction, 20 min after induction, and 30, 60, 90, 360 min and 24 h after skin incision. All these measurements were by radioimmunoassay.

A progressive and significant decrease of cortisol ($P < 0.01$) was observed in groups II and IV to values not exceeding 300 nmol litre^{-1} in both groups, at the end of operation. In groups I and III, cortisol remained at basal values during operation, and 24 h later there was a significant decrease in the values ($P < 0.05$). There were no significant changes in mean PA concentrations when compared with control values, being lower in groups I and II 24 h after operation. There were high ACTH secretion peaks followed by moderate increases of cortisol but not of PA in more than 80% of the total hip arthroplasty colour. On the other hand, in groups II and IV the mean ACTH values were lower than basal in 22 of the 24 patients. The mean GH and prolactin plasma concentrations were significantly greater in groups I and III. It could be said that the pituitary–adrenocortical response to surgical stress was abolished in those patients undergoing inguinal hernioplasty. In contrast, the afferent neurogenic impulses were not completely blocked in the total hip arthroplasty group. It must be stressed that the inhibition of adrenocortical function lasted longer and coincided with the duration of analgesia when the etidocaine–buprenorphine combination was used.

RESPIRATORY DEPRESSION WITH BUPRENORPHINE: ONSET TIME AND REVERSAL

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Buprenorphine, a synthetic analgesic structurally similar to morphine and a partial agonist, is being promoted for its long duration of action (Rolly and Versichelen, 1967). Its potential for severe respiratory depression is uncertain (Orwin, 1977) and the onset of action appears similar to other powerful analgesics.

We have used a new approach to assess some of these factors on patients. A standard premedication (diazepam 10 mg), induction with thiopentone, tracheal intubation after suxamethonium and spontaneous respiration with 1% halothane in 66% nitrous oxide in oxygen was administered in near equilibrium state. The analgesic was injected i.v. either in a single bolus or subsequently in other patients in a logarithmic increasing dose pattern at intervals derived from analysis of single-dose studies. End-tidal carbon dioxide concentration, respiratory frequency and tidal volume were measured.

Using this technique, we have demonstrated a slow onset of action, the peak effect being considerably delayed. We have also measured the degree of reversal of this depression with naloxone.

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RESPIRATORY DEPRESSION DURING ENFLURANE ANAESTHESIA CORRECTED BY ALMITRINE IN THE DOG BUT NOT IN HUMANS

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While assisted or controlled ventilation is widely used in anaesthesia, adequate spontaneous breathing would be of advantage in avoiding the circulatory effects of increased mean intrathoracic pressure and allowing for anaesthesia without hypercarbia under circumstances other than those found in well-equipped operating theatres. We attempted to achieve adequate spontaneous ventilation under enflurane anaesthesia by the administration of a respiratory stimulant, almitrine.

In a preliminary study (Morin, Landais and Sansoy, 1980) in dogs under pentobarbitone anaesthesia, Pa_{CO_2} increased from 6.3 ± 0.47 to 8.45 ± 0.3 kPa after 15 min of 2% enflurane inhalation. When almitrine was given from the start of enflurane inhalation, Pa_{CO_2} increased from 6.4 ± 0.4 to 6.8 ± 0.4 kPa, a highly significant difference.

In 15 patients undergoing orthopaedic surgery with enflurane anaesthesia with spontaneous breathing (after induction with i.v. pentobarbitone 5 mg kg^{-1}, 3% enflurane for 15 min and 2% thereafter), Pa_{CO_2} increased from an average of 4.8 ± 0.2 kPa to 6.0 ± 0.24 kPa 15 min after the start of enflurane inhalation (before the start of surgery).

In 15 similar patients, almitrine 1 mg kg^{-1} was given in 250 ml of 5% glucose before the inhalation of enflurane. In 10 additional patients, the almitrine infusion was started at the same time as the administration of enflurane. The average Pa_{CO_2} in the 15 patients in whom almitrine was given before enflurane was 4.68 ± 0.37 before and 5.9 ± 0.52 kPa 15 min after the start of enflurane anaesthesia.

When enflurane was given with the almitrine infusion, the values were 4.65 ± 0.25 before anaesthesia and 6.4 ± 0.55 kPa at 15 min. The differences are not significant when compared with the control group. There were no significant differences at 35 and 55 min in either Pa_{CO_2} or pH. No significant differences were found in Pa_{CO_2} at any time.

The respiratory depression observed in patients breathing spontaneously during enflurane anaesthesia is of tolerable magnitude for average adults without respiratory disease. This respiratory depression is not corrected in men by almitrine 1 mg kg^{-1}, whether given before or at the start of enflurane inhalation.

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DIAZEPAM REDUCES LOWER OESOPHAGEAL SPHINCTER PRESSURE

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Two previous studies on the effect of i.v. diazepam on the lower oesophageal sphincter presure showed that, with a dose of 2.5–10 mg, a decrease occurred (Hall et al., 1975), but that with a dose of 20 mg, sphincter pressure increased (Weiruch et al., 1979). In view of these conflicting data and the fact that diazepam is generally administered orally for premedication, a randomized double-blind study has been performed on nine healthy volunteers receiving either diazepam 10 mg orally or placebo. Measurements were made of gastric pressure, sphincter pressure and barrier pressure (sphincter–gastric pressure) from 45 to 75 min after ingestion of the capsules.

The results showed that diazepam produced a small but significant decrease in barrier pressure. There was no apparent correlation between plasma diazepam concentrations and barrier pressure. Some subjects with marked drowsiness exhibited a considerable reduction in barrier pressure of more than 50%. It is concluded that premedication with oral diazepam may produce increased predisposition to regurgitation, but that because of considerable variation in response, prediction of susceptible individuals is difficult.

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MONITORING OF E.E.G. AND E.M.G. DURING ANAESTHESIA

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Insufficient attention has been paid to the routine monitoring of the central nervous system and muscle tension during general anaesthesia. The lack of suitable instrumentation coupled with difficulty of e.e.g. interpretation have been among the discouraging factors. Recent technological advances have made continuous quantitative e.e.g. and e.m.g. recording possible during surgery. Harmel, Klein and Davis (1978) introduced frontal muscle e.m.g. activity recording as an index of paralysis, and arousal caused by surgical stimulation, under general anaesthesia.

To assess the depth of anaesthesia and the degree of paralysis and to observe early warning of impending brain ischaemia we have been using combined e.e.g. and e.m.g. monitoring in the following way:

A quantitative e.e.g. was recorded and two main parameters—the total energy (from frequencies 1–30 Hz) and the mean frequency (for frequency band 2–12 Hz)—were monitored. The e.m.g. activity from m. frontalis has been used to monitor various states of anaesthesia. The e.m.g. was analysed by means of FFT and, exploiting these data, the total energy content from frequencies 1–30 Hz was calculated. To account for the large variations in e.m.g. energy during the awake state and anaesthesia, and to provide proper sensitivity during anaesthesia, extracted energy values were logarithmically compressed before display. The continuous monitoring of e.e.g. and e.m.g. parameters displayed on a videoscreen in the operating theatre during general anaesthesia has, in our preliminary study, been shown to be valuable in assessing the quality of anaesthesia and the reactions of patients to stressful stimuli. A common finding has been an instantaneous increase of e.m.g. energy at intubation, skin incision and during other sensory stimuli. The changes in e.e.g. and e.m.g. usually occurred with the responses from the cardiovascular system (increase of arterial pressure and heart rate). The trend of increase in e.m.g. activity serves as a useful sign of lightening of the level of anaesthesia and warns of an impending reaction to surgical stimuli. This information has proved to be useful for the anaesthetist to adjust the level of anaesthesia. The monitoring of the brain activity (during open heart surgery) with the technique we have used has shown typical e.e.g. reactions to hypoxia consequent upon a decrease in cerebral perfusion pressure.

The preliminary results of these studies in e.e.g. and e.m.g. monitoring will be discussed in the light of individual case reports.

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HETEROZYGOTES FOR ATYPICAL CHOLINESTERASE

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The commonest genetically-determined abnormality of cholinesterase is the atypical. The part played by the homozygous version of this abnormality is well known. Heterozygotes ought to be much commoner (about 1 : 25 of the population among Caucasians). Yet only relatively few heterozygotes are found by cholinesterase services among patients with prolonged apnoea after suxamethonium. There were 17 such among 237 patients with prolonged apnoea investigated by the Manchester service in the course of 8 years. Perhaps the vast majority of heterozygotes pass unnoticed because the extent of the resulting prolongation of the action of suxamethonium is slight. To this end the sera of 29 of 332 patients undergoing electroplexy who had a minor prolongation of the action of suxamethonium (more than 4 min apnoea) were investigated biochemically. Eight proved to be heterozygotes for the usual and the atypical gene. Two were heterozygotes for the usual and the fluoride-resistant gene. These figures approximate to the expected frequency of these abnormalities.

INTUBATING CONDITIONS WITH ORG NC 45

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Although suxamethonium provides near ideal conditions for intubation, it suffers from several disadvantages based on its depolarizing mode of action. These include hyperkalaemia, cardiac arrhythmia, muscle pains and increase in intraocular pressure. There is clearly a need for a rapid and short-acting non-depolarizing muscle relaxant. Org NC 45 is a new non-depolarizing muscle relaxant shown to have a faster onset of action than other drugs of this group, and a shorter duration of action (Bowman, 1980). This study reports the intubating conditions with this agent compared with pancuronium and suxamethonium.

Adult patients of ASA grades 1 and 2 were studied. Premedication consisted of diazepam 10–15 mg given orally and induction was with thiopentone 5–6 mg kg^{-1}. Subsequent to the loss of eyelash reflex Org NC 45 0.1 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} or suxamethonium 1.0 mg kg^{-1} was administered rapidly and the lungs ventilated with, or the patient allowed to breathe, 70% nitrous oxide in oxygen. Intubating conditions were assessed at 30, 60, 90 or 120 s according to a four-point scale (Young, Clarke and Dundee, 1975) in groups of 20 patients. Jaw and cord relaxation were also noted.

Neuromuscular transmission was monitored in some patients using a peripheral nerve stimulator (Myotest, Biometer). Note was also made of changes in heart rate and arterial pressure during the induction phase.

In the doses used only suxamethonium provided ideal intubating conditions at 30 s. At all other times Org NC 45 provided better conditions in comparison with pancuronium and intubation could be carried out with the former in most patients between 60 and 90 s.

Neuromuscular transmission was completely blocked in about 3.5 min with Org NC 45, but intubation could be carried out earlier. No significant increases in heart rate were observed after Org NC 45.

Intubating conditions were also evaluated in a separate group of 20 patients using Org NC 45 in a dose of 0.15 mg kg^{-1}. A marked improvement in conditions was found without any associated clinical problems.

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REVERSIBILITY BY NEOSTIGMINE OF AN ORG NC 45 NEUROMUSCULAR BLOCKADE UNDER HALOTHANE AND ENFLURANE ANAESTHESIA IN THE CAT

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Several studies have shown the potentiation by halothane and enflurane of neuromuscular blockade by non-depolarizing muscle relaxants. The new short-acting muscle relaxant Org NC 45 is no exception to this rule. The influence of these inhalation agents on the reversibility by an esterase inhibitor of such a block has not yet been studied.

In 17 cats under light anaesthesia with i.v. thiopentone the ischial nerves were stimulated supramaximally and the contractions of m. tibialis were recorded; 80–90% neuromuscular blockade was produced by a steady-state infusion of Org NC 45 for at least 30 min.

In five cats this block was preceded by 30 min inhalation of 1 MAC of halothane (0.73%) and in six cats of 1 MAC enflurane (1.68%) which continued during the whole experiment.

After 30 min of steady-state block neostigmine 20 μg kg^{-1} was given to all cats while the infusion was continued and the following were measured: percentage reversal of the block; speed of onset of the block; time of return of the block to 50% and to the previous % of steady-state block.

The third group of six cats was used as the controls and received no inhalation agent.

There was a statistically significant reduction in the amount of Org NC 45 necessary to cause a steady state 80–90% block in the enflurane group compared with control. No statistically significant difference existed between the halothane and the control group, although a tendency to a decreased amount was noted. No significant difference existed in the onset of the antagonism, the amount of reversal and the times for return to 50% block.

The enflurane group showed a significant prolongation of the time for return to the previous percentage of steady-state block.

It is concluded that the same degree of neuromuscular block caused by Org NC 45 under light barbiturate anaesthesia supplemented by 1 MAC halothane and enflurane and under light barbiturate anaesthesia alone are equally reversed. The total effect of neostigmine lasted longer during enflurane anaesthesia.

DRUG INTERACTION WITH LOCAL ANAESTHETICS

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A high rate of regional anaesthetic failures was observed in orthopaedic surgery in patients suffering from rheumatic joint diseases. This observation was thought to be a result of interaction of long-term treatment with antirheumatic and local anaesthetic drugs. Membrane-stabilizing drugs such as ethanol, antirheumatics and local anaesthetics produce an expansion of biomembranes by increasing the fluidity of the lipid bilayer (Zeil and Krupp, 1976; Nuhn, Frenzel and Arnold, 1979). Under chronic exposure to ethanol this membrane effect exhibits tolerance (Chin and Goldstein, 1977).

In a prospective study of 162 patients of both sexes undergoing orthopaedic surgery of the lower limbs and receiving daily treatment with antirheumatic drugs for a period of at least 6 months and with a daily alcohol intake of at least 80 g spinal anaesthetics were performed with an average volume of 2 ml of 0.5% bupivacaine.

The latency and duration of analgesia was noted in all dermatomes relevant to the operation. The response to this low-dose spinal anaesthesia was classified: ***normal response*** = latency (L) up to 10 min, minimal duration (D) of analgesia 2 h; ***reduced response*** = L 11–20 min or D less than 2 h, or both; ***total failure*** = no analgesia.

Ninety-two patients were without long-term treatment or taking ethanol (group A), 70 patients were receiving long-term treatment or taking ethanol, or both (group B), and 36 patients received indomethacin treatment (group C). The low dose of bupivacaine produced the following effects (fig. 1): group A = 5% total failure, 3% reduced response, 4% deficient spread (L greater than 10 min in higher dermatomes only); group B = 32% total failure, 4.5% reduced response, 4% deficient spread; group C = 42% total failure, 39% reduced response, 5% deficient spread.

There was no correlation between age, body weight, height, dose, segmental spread and the number of partial or total failures. The only positive correlation was between long-term treatment and ethanol.

This interaction involves drugs of widely differing chemical structure and pharmacological properties. It may be a result of their common action on the fluidity of membranes for which Chin and Goldstein (1977) had found evidence for the existence of a "non-specific tolerance mechanism".

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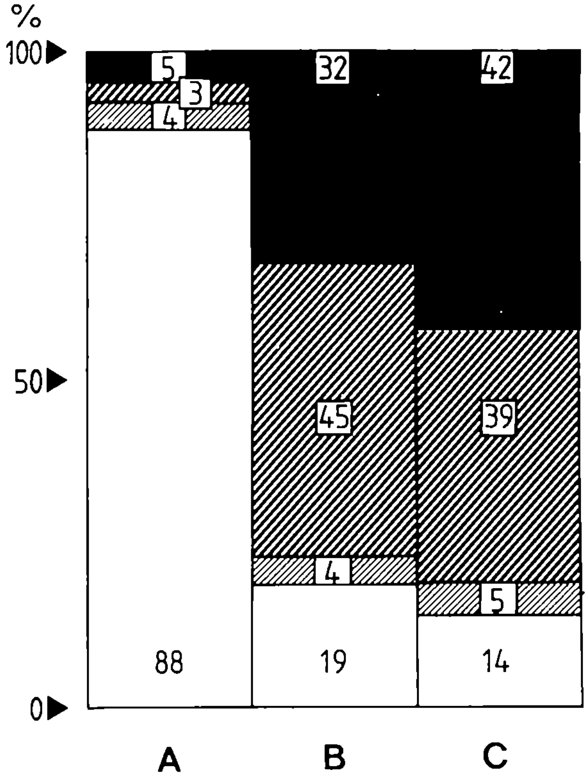

FIG. 1. Long-term treatment and response to low-dose spinal anaesthesia. A: Control group A without treatment or alcohol (n = 92). B: Group B with long-term treatment or alcohol (n = 70). C: Part of group B treated with indomethacin only (n = 36). □ = Normal response; ▨ = deficient spread; ▨ = reduced response; ■ = total failure.

EFFECT OF PREMEDICANTS ON THE CARDIOVASCULAR SYSTEM: IS PREMEDICATION WITH ATROPINE NECESSARY?

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The effect of atropine alone, Thalamonal (droperidol plus fentanyl) alone and in combination on the cardiovascular system was studied in three groups of patients. Group I received atropine 0.6 mg i.v., group II received Thalamonal 2 ml i.v. and group III received both atropine and Thalamonal i.v., all given a few minutes before induction of anaesthesia. Heart rate (HR) and systolic arterial pressure (AP) were recorded (a) before any drug was given, (b) 5 min after i.v. premedication, (c) when intubation was completed and (d) 5 min, (e) 10 min and (f) 15 min after intubation. E.c.g. (lead II) was monitored with an oscilloscope throughout the procedure and recorded on paper before administration of the premedication and during intubation.

In group I AP increased significantly during intubation (P_{a-c} <0.005) and HR was constantly faster (P_{a-b} <0.001; P_{a-c} <0.001; P_{a-d} <0.005; P_{a-e} <0.01 and P_{a-f} <0.02). During intubation cardiac arrhythmias were significantly more frequent in this group compared with group II (P_{I-II} <0.05). In group II no significant changes in AP were noticed and HR increased only during intubation (P_{a-c} <0.05); the frequency of arrhythmias was significantly less. In group III no significant changes in AP were noticed and HR increased significantly 5 min after i.v. injection of the premedicants and during intubation (P_{a-b} <0.001; P_{a-c} <0.01). Cardiac arrhythmias did not differ significantly compared with group I ($0.10 > P > 0.05$).

Cardiovascular stability appears to be maintained and cardiac arrhythmias are frequent when atropine is not given as a premedicant. Thalamonal seems to attenuate the effect of i.v. atropine administration on the cardiovascular system.

RADIOCARDIOGRAPHIC EVALUATION OF INDUCTION OF NEUROLEPTANAESTHESIA IN PATIENTS WITH MITRAL STENOSIS

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Selected haemodynamic indices before and after induction of anaesthesia were measured in patients undergoing commissurotomy. We used a mobile radiocardiography assembly. Indium m–113m In, injected in a single bolus to the catheter introduced via the basilic vein to the right atrium, was used as a marker. Only patients aged 36–42 yr were selected for study. Two studies were performed in each patient. The first served as control and took place 12 h before anaesthesia, the second 5 min after induction of anaesthesia. For induction of anaesthesia we gave droperidol, fentanyl and thiopentone with pancuronium. After induction and during radiocardiographic examination the lungs were ventilated with a mixture of nitrous oxide and oxygen in a ratio of 3 : 1 in a semi-closed circuit.

A significant increase in pulmonary blood volume and pulmonary mean transit time occurred after induction of anaesthesia. This is probably the result of an influence of the drugs used and of an increased concentration of oxygen in inspired mixture of the gases.

ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION FOLLOWING INDUCTION WITH ALTHESIN

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Echocardiography is a sensitive non-invasive technique which provides direct visual information concerning left ventricular (LV) function. Using M-mode echocardiography, we report the cardiovascular effects of Althesin.

Ten healthy unpremedicated patients without cardiac disease, ranging in age from 24 to 65 yr, who were to undergo elective surgery were studied. Each series of measurements consisted of systolic and diastolic arterial pressure (SAP and DAP), heart rate (HR), M-mode echoes of the left ventricle. Derived data included: systolic index (SI), ejection fraction (EF), percentage of circumferential fibre shortening (%R), left ventricular end diastolic volume index (LVEDVI) percentage of systolic thickening of the interventricular septum (%IVS), percentage of systolic thickening of posterior wall (%PW).

Measurements were made with the patient awake (control) and 1, 3, 5 and 10 min following i.v. administration (injection time = 30 s) of Althesin 0.1 ml kg^{-1}.

Echocardiographic findings demonstrated a decrease in total and segmental ventricular performance following induction with Althesin (table I). These effects may be related to the alteration of myocardial contractility or to the diminished preload. In favour of the preload effect, we noted, in four patients, a marked decrease in LVEDVI with parallel decrease of %R, %IVS and systolic index. These were unchanged in the other six patients. These data suggest that the decrease in preload is the main cause of the echocardiographic changes following administration of Althesin.

TABLE I. *Echocardiographic measurements and derived data.*
P <*0.05*; **P <*0.02*; ***P <*0.01 from control value*

	Awake	1 min	3 min	5 min	10 min
SAP (mm Hg)	120 ± 8	105 ± 13***	119 ± 20	114 ± 17	117 ± 12
DAP (mm Hg)	81 ± 9	67 ± 13**	78 ± 17	73 ± 15	74 ± 15
HR (beat min^{-1})	71 ± 12	85 ± 10***	90 ± 13***	85 ± 11*	84 ± 12
LVEDVI (ml m^{-2})	75 ± 29	70 ± 19	60 ± 22	57 ± 22*	73 ± 25
SI (ml m^{-2})	47 ± 18	41 ± 8	35 ± 16	33 ± 15**	42 ± 18
EF (%)	63 ± 11	64 ± 8	58 ± 8	58 ± 9	57 ± 8*
%R	35 ± 8	33 ± 7	31 ± 6	31 ± 6	30 ± 6*
%IVS	33 ± 21	16 ± 15*	17 ± 17	20 ± 30	25 ± 13
%PW	74 ± 17	75 ± 31	62 ± 28	64 ± 21	72 ± 23

ON THE RELATIONSHIP BETWEEN END-DIASTOLIC CARDIAC SIZE AND VENTRICULAR FUNCTION UNDER INCREASING DOSES OF ENFLURANE IN INTACT, CHRONICALLY INSTRUMENTED DOGS

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While enflurane is generally held to depress myocardial contractility, its overall effects on left ventricular (LV) function are less clear. The goal of the present study was to analyse the relationship between LV end-diastolic fibre length and LV stroke work (the Frank–Starling relation) and thereby to separate effects on loading conditions from direct effects on myocardial contractility under the influence of enflurane.

Five dogs were chronically implanted with miniature solid-state LV pressure transducers and with aortic and left and right atrial catheters. A pair of ultrasonic diameter transducers was implanted on opposing endocardial surfaces. Experiments were performed 2–7 weeks after surgery when the animals were resting quietly without premedication. Enflurane was given in concentrations of 2 and 4 vol% with ventilation held constant. Experiments were repeated on a separate day either with spontaneous ventilation or after beta- (propranolol 1 mg kg^{-1} i.v.) or combined beta- and cholinergic (atropine 0.15 mg kg^{-1} i.v.) blockades or with heart rate held constant (right ventricular pacing). For the calculation of internal stroke work, instantaneous LV pressure and LV diameter signals were digitized, and the area of LV pressure–diameter loops was computed as an index of work.

As has been shown previously, enflurane led to a progressive dose-dependent decrease in myocardial contractility (table I). This was associated with a decrease in LV stroke length and in LV stroke work. However, the decrease in contractility was not associated with an increase in LV preload, that is LV end-diastolic diameter was decreased by 2 vol% while it returned towards control with 4 vol%. Similar results were obtained after beta-receptor, combined beta-receptor and cholinergic blockades, with heart rate held constant and while the animals were breathing spontaneously. Thus, the negative inotropic effect of enflurane is modified by a decrease in both preload and afterload with 2 vol% and a marked decrease in afterload with the greater concentration. Under steady-state conditions neither controlled respiration with IPPV, secondary reflex effects, nor the increase in cardiac rate appear to be of major significance for the observed changes in LV function.

TABLE I. *Changes (%) in myocardiac indices (mean± SD).* *$P < 0.01$

	Control	2 vol%	4 vol%
LV end-diastolic	37.4	−7.5*	−2.3
diameter (mm)	±3.2	±1.1	±2.4
LV stroke	7.3	−31.0*	−42.0*
shortening (mm)	±1.8	±8.7	±12.7
LV systolic	117.0	−21.8*	−31.5*
pressure (mm Hg)	±4.4	±7.6	±7.8
LV end-diastolic	9.0	−19.2*	14.0*
pressure (mm Hg)	±1.4	±6.3	±3.2
LV stroke work	906.4	−50.8*	−63.1*
(mm . mm Hg)	±190.2	±15.8	±14.2
Mean arterial	93.3	−25.5*	−37.0*
pressure (mm Hg)	±7.3	±6.2	±6.7
LV dP/dt_{max}	2810.0	−28.8*	−52.6*
(mm Hg s^{-1})	±309	±7.2	±9.4
LV velocity	65.2	−18.6*	−35.6*
(mm s^{-1})	±5.8	±3.4	±3.7
Heart rate	86.2	35.2*	44.4*
(beat min^{-1})	±6.1	±12.5	±11.0

DEXTRAN *V.* ALBUMIN HAEMODILUTION IN HIP SURGERY

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At this hospital, haemodilution is used for patients undergoing hip arthroplasty. Albumin solution is used for dilution, but the cost of its preparation is so great that less expensive plasma substitutes have been tested. The present study was designed to compare the effects of haemodilution with dextran 60 on intra- and postoperative haemodynamics and oxygen transport, in nine patients, with those observed in eight patients undergoing haemodilution using 4% albumin solution. Intra- and postoperative blood loss were compared between the two groups. In both groups, the bled volume was calculated to achieve a haemoglobin concentration in the range of 7–9 g dl^{-1}. Blood was withdrawn just before operation under anaesthesia. Simultaneously, a volume of dextran 60 solution or 4% albumin solution, equal to that of the shed blood, and an equal volume of lactated Ringer solution were infused. The shed blood was reinfused after the end of the surgical procedure. Arterial and pulmonary artery pressure were recorded continuously. Cardiac output was determined by thermodilution. Arterial and venous oxygen content were measured directly by colorimetry. The measurements were made before induction, after haemodilution, and 5, 60 and 120 min after the end of anaesthesia. The results are shown in table I.

In both groups, a significant increase was observed at 5, 60 and 120 min after the end of anaesthesia, compared with the initial values, in the following: heart rate, cardiac index, oxygen consumption, heart rate × systolic arterial pressure product (an indirect index of myocardial oxygen consumption). Systemic vascular resistance was significantly reduced in both groups at each measurement after haemodilution. The arteriovenous oxygen content difference was unchanged in both groups. These hyperkinetic haemodynamic changes were significantly more marked in patients undergoing haemodilution with albumin solution. Intra- and postoperative blood loss were not statistically different between the two groups. These results suggest that dextran 60 can be a good alternative for haemodilution compared with albumin solution. The haemodynamic effects of dextran are less prolonged than those of albumin solution. Operative blood loss was not influenced by dextran haemodilution.

TABLE I. *Comparative effects of haemodilution using dextran (D) and albumin (A) solutions on haemodynamics, oxygen transport and haemoglobin concentration (mean values).* **Group D* v. *group A*, $P < 0.01$. *MAP = mean arterial pressure (mm Hg); CI = cardiac index (litre m^{-2}); PWP = pulmonary wedge pressure (mm Hg); ($Ca_{O_2} - Cv_{O_2}$) = arterio–venous oxygen content difference*

	MAP		CI		PWP		($Ca_{O_2} - Cv_{O_2}$)		Hb (g dl^{-1})	
	D	A	D	A	D	A	D	A	D	A
Control	85	95	3.5	3.9	4	6	4.1	3.8	12.7	13.8
After dilution	60	100	3.2	3.1	10	11	3.2	3.8	7.8	8.7
After anaesth.										
5 min	95	100*	5.3	5*	8	9	—	—	7.3	7.2
60 min	95	105*	4.9	6*	8	15*	—	—	—	—
120 min	100	100*	4.9	5.8*	9	15*	3.8	3.9	8.6	8.5

MICROCIRCULATORY EFFECTS OF DELIBERATE HYPOTENSION

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Sodium nitroprusside (SNP), widely used to induce hypotension, is not free of adverse effects. Experimental studies have shown that SNP-induced hypotension (mean arterial pressure 40 mm Hg) is accompanied by tissue hypoxia in liver and skeletal muscle. The changes in local P_{O_2} values suggested a redistribution of microcirculatory blood flow. Therefore, the present study was aimed at analysing effects of SNP hypotension on all vessel segments of the microvasculature. Data obtained with SNP were compared with results of deliberately induced hypotension with nitroglycerin (NTG). A dorsal skin-flap chamber was implanted in 16 hamsters, allowing for microcirculatory studies in s.c. tissue and skin muscle. Systemic arterial pressures and heart rate were measured by means of permanent catheters in the carotid artery

TABLE I.

	Condition			
	Control	70	40	10 min
L_A (cm^{-1})				
SNP	199.0 ± 9.3	178.5 ±12.7	136.8 ±10.0	74.3 ± 9.2
NTG	210.8 ±15.1	235.4 ±17.4	189.5 ±10.5	178.3 ±11.5
R_{ven} (PRU 10^6)				
SNP	0.87± 0.24	1.12± 0.28	1.25± 0.27	1.49± 0.32
NTG	0.81± 0.20	0.61± 0.17	0.52± 0.11	0.68± 0.20

and jugular vein. Seventy-two hours after the initial surgery, hamsters were anaesthetized with enflurane 1 MAC and hypotension was induced by infusion of SNP or NTG. Measurements were made before hypotension (control), at MAP 70 mm Hg (70) 40 mm Hg (40) and 10 min after the end of drug infusion (10 min). The microcirculation was studied by means of intravital fluorescent microscopy after i.v. injection of FITC-Dextran 150 and quantitative video techniques, a platinum multiwire electrode for local P_{O_2} measurements and the servonulling technique for measurements of microvascular pressures.

A decrease in density of erythrocyte-perfused capillaries (L_A, table I) in skin muscle accompanied by severe tissue hypoxia was observed during and after SNP-hypotension, whereas L_A and local P_{O_2} remained unchanged, when NTG was used. SNP dilated predominantly precapillaries. NTG dilated the feeding and drainage vessels. While the segmental resistance of arterioles was decreased with both drugs, the segmental resistance of venules (R_{ven}; table I) increased with SNP and decreased with NTG. During SNP hypotension at MAP 40 mm Hg, 55% of the arteriolar blood volume coursed through arterio–venous shunts. The present study provides evidence that the resistance in venules was increased during SNP-hypotension with capillary perfusion and density diminished and 55% of blood was redistributed through a–v shunts.

ARTERIAL HYPERTENSION AS CONTRIBUTORY FACTOR TO THE RISKS FROM ANAESTHESIA AND SURGERY IN PATIENTS WITH MYOCARDIAL INFARCTION

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At the last World Congress of Anaesthesiologists (Hamburg, September 1980) our results of a retrospective study on the morbidity and mortality from anaesthesia and surgery in patients with coronary heart disease were presented.

The study was conducted on a population of 17 170 patients, aged more than 30 yr, who underwent anaesthesia for surgery or a diagnostic procedure over a period of 7 years (1973–79). Five hundred and ninety-three patients had a previous myocardial infarction and 34 of them (5.73%) experienced, within the 1st week after operation, a new myocardial infarction with high mortality (53%).

The purpose of this study was to investigate the contribution of coexisting arterial hypertension to the frequency of postoperative re-infarction and its mortality rate by a further review of the hypertension of the group of 593 patients with preoperative myocardial infarction. Patients were considered to be hypertensive with a systolic arterial pressure greater than 160 mm Hg and a diastolic pressure greater than 100 mm Hg. Of the 593 patients, 385 were hypertensive and 25 developed myocardial infarction after operation, with a mortality rate of 60%, only nine patients from the remaining 208, with no arterial hypertension, experienced myocardial re-infarction and a lower mortality rate (33%).

Our findings led to the assumption that arterial hypertension might be considered as a contributory factor to the high risks from anaesthesia and surgery in patients with myocardial infarction.

ALTHESIN AND ALFENTANIL FOR MINOR SURGERY

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Alfentanil is a novel narcotic analgesic with a very short duration of effect. Althesin is an i.v. anaesthetic with a short action and little cumulation, which is extensively used for total i.v. anaesthesia, particularly for minor surgery. A combination of alfentanil and Althesin in a fixed ratio of 2 mg : 10 ml (in 11 ml) was used to provide anaesthesia for 50 patients (ASA I or II) undergoing minor surgery. Twenty-five patients were women undergoing minor gynaecological procedures, 15 patients underwent cystoscopy and 10 patients vasectomy or other minor surgery.

No premedication was given. Anaesthesia was induced with 2–3 ml of the mixture according to the patient's age and weight, given over 30 s. Supplements of 0.5 or 1 ml were given over 20 s in anticipation of inadequate anaesthesia. The patients breathed air spontaneously, with an airway if required. The pulse wave-form was monitored continuously, and respiratory rate and pupil size every 2 min. Other observations were the occurrence of side-effects, time to wakening after the last injection, and the degree of movement in response to surgery.

The mean duration of anaesthesia was 13 min and of surgery 9 min. The mean induction dose was 2.7 ml. The first supplementary dose of alfentanil–Althesin was given after a mean interval of 2.2 min, thereafter the mean rate of use was 0.32 ml min^{-1} (mean total supplement 3.45 ml). The mean time to compliance with the request "Stick out your tongue" was 5.2 min after the last injection of anaesthetic, 2.9 min after the end of operation.

Clinical efficacy was good, movement in response to surgical stimulation being the main problem in 36% of cases. Of these, movement was so slight as to be unnoticed by the surgeon in 14%, and in no case was the method of anaesthesia abandoned. Clinically important respiratory depression occurred and ventilation was assisted, without difficulty, in 12% of patients. There was no problem with respiratory depression after operation, and no case of unduly prolonged recovery. Postoperative nausea or vomiting were reported on only two occasions.

The addition of 2 mg of alfentanil to 10 ml of Althesin adds an analgesic component to the i.v. anaesthetic; the mixture provided generally good anaesthesia for minor surgery, and allowed excellent, rapid recovery. On a similar group of patients, this technique gave much better results than that previously reported (Kay and Stephenson, 1980).

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TRANSCUTANEOUS P_{O_2} CONTINUOUS RECORDING IN PAEDIATRIC ANAESTHESIA

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Since November 1979 a transcutaneous P_{O_2} (TcP_{O_2}) monitor has been used by the paediatric team of the Anaesthesia Department of the Hôpital des Enfants Malades. The sensor, including a Clarke electrode, has been modified to eliminate the electrical interference and the effect of nitrous oxide.

Seventy-five recordings have been made during anaesthesia for general surgery (39 patients), neurosurgery (15 patients) and endoscopy (21 patients). The age of the patients ranged from 4 h to 16 yr. Anaesthesia consisted of halothane (47 patients) and neuroleptanalgesia (18 patients). In 60 patients the trachea was intubated and in 63 the lungs were artificially ventilated. The average total time of recording was 3 h (from 40 min to 9.3 h).

Technical problems occurred during recording which were not easy to resolve in a busy operating theatre. About 20 min were needed to prepare and calibrate the sensor. The sensor became dislodged several times when moving the patient for positioning or when dressing the wound. The recording was often disturbed by surgical manipulations.

TcP_{O_2} recordings allowed the authors to visualize at once the consequences of induction of anaesthesia, intubation, tracheal suction and extubation. Sudden disconnection of the respirator could be detected immediately. In cases of artificial ventilation the variations of P_{O_2} could be read at once and the ventilation readjusted. At the end stage of anaesthesia it was possible to monitor the recovery of spontaneous ventilation and the progressive change to F_{IO_2} 0.20. Thus we could decide if the lungs should continue to be ventilated artificially.

In repair of diaphragmatic hernia, laparoscopy or omphalocele, the authors could observe the effect of abdominal retraction. In fibreoptic tracheobronchoscopy they could determine how long and how much hypoxia could be tolerated without risk.

In babies younger than 1 yr (43 measurements) the relationship between TcP_{O_2} and capillary P_{O_2} showed a correlation of $r = 0.86$.

When TcP_{O_2} and TcP_{CO_2} recordings were combined (eight patients) better control of the ventilatory management was possible.

CARDIOVASCULAR RESPONSES TO COMBINED APNOEA AND FACE IMMERSION IN EXERCISING MAN

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Man is a poor diver compared with a seal which can be submerged for almost 30 min without any harm. Nevertheless, there is at least one detailed report of successful resuscitation of a 5-yr-old boy after 40 min of total submersion in cold water (Siebke et al., 1975). This suggests that oxygen-conserving cardiovascular adjustments exist, and that they can be of major importance in man.

Several investigators have noted that humans, like seals, develop bradycardia and peripheral vasoconstriction during apnoea with face immersion (AFI). Direct measurements of changes in cardiac output (CO) and systemic vascular resistance (SVR) in this situation are, however, non-existent. Such information is essential to emphasize the biological mechanisms which make possible successful resuscitation after near drowning.

Changes in central haemodynamic variables during apnoea with face immersion in ice water were studied. The experiments were performed on two of us (L.B. and A.H.) while exercising on an ergometer bicycle at constant work load. An indwelling Swan–Ganz catheter allowed measurements of pulmonary arterial pressure (P_{PA}), right atrial pressure (P_{RA}) and cardiac output (CO). The last index was determined by utilizing a thermodilution technique. Systemic arterial pressure (SAP) was measured via a radial artery cannula. Heart rate (HR) was obtained from the e.c.g. All indices were recorded during spontaneous ventilation (control) and at cessation of AFI.

During AFI, HR and CO gradually decreased to about 50% of the control values. Correspondingly there was a twofold increase in SBP, SVR, P_{PA} and P_{RA} compared with control values.

These studies have revealed that humans have elements of the same cardiovascular adjustments to apnoea and face immersion as the aquatic vertebrates like the seal, although much less pronounced.

PULMONARY FAT EMBOLISM SYNDROME: CLINICAL, PATHOLOGICAL AND THERAPEUTIC ASPECTS

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Pulmonary fat embolism (PFE) is seldom diagnosed in orthopaedic surgery, but its severe form may lead to death. The syndrome is difficult to study because its signs and symptoms are varied and the number of established cases is small. Some authors even deny its existence. Our studies were mainly based upon clinical criteria, e.c.g. and lung x-ray findings. We were able to identify three major clinical presentations corresponding to

Sevitt's classification. The need for a more reliable and objective diagnosis caused us to use the Bschor and Haasch Laboratory analysis of fat globules in circulating blood seen under fluorescent microscopy.

A total of 38 patients was examined: 26 had skeletal trauma and the majority of these underwent surgery for bone repair; 12 underwent elective surgery. Only two patients developed symptoms and signs of PFE. Blood samples were taken only once (peripherally during surgery) in 13 patients, and at least twice (from the femoral vein, before and after surgery) in the other 25 patients. Samples were always taken double-blind and were controlled against peripheral blood of a normal subject in 23 cases with central *v.* peripheral blood of the same patient in 15 cases. Samples were positive in 69% of (peripheral) samples, in 92% of femoral samples during surgery, in 56% of femoral samples before surgery and in 22% of the controls. In 65% the central venous sample was positive against a negative peripheral sample.

Our results seem to demonstrate that this method is not as valuable as it seemed at first. Criteria that we, and other authors, considered important in the past still remain the most reliable. A recent revision of all our 1980 cases was carried out on the basis of these criteria and showed that correct prophylaxis with phosphatidylcholine, dextran and aprotinine is still a successful and efficient method for reducing the frequency and gravity of PFE.

EFFECTS OF ALTERATIONS IN BLOOD-GAS TENSIONS ON THE RESPONSIVENESS OF THE CEREBRAL CIRCULATION 1 WEEK AFTER THE INDUCTION OF SUBARACHNOID HAEMORRHAGE

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Studies in the baboon have shown that the responsiveness of the cerebral circulation to alterations in systemic arterial pressure was impaired 1 week after the induction of an artificial subarachnoid haemorrhage (Pickard et al., 1979). The present report describes the effects of alterations in arterial carbon dioxide tension and arterial oxygen tension on cerebral blood flow (CBF) in the same animal model.

An artificial subarachnoid haemorrhage was produced in five anaesthetized baboons (5.5–6.5 kg) by the injection of fresh autogenous blood (0.75 ml kg^{-1}) to the suprachiasmatic cistern via a needle inserted percutaneously through the optic foramen without enucleation of the orbit. One week later the animals were re-anaesthetized (thiopentone 7.5 mg kg^{-1} i.v.; 70% nitrous oxide in oxygen; phencyclidine 4 mg every 30 min), ventilation was controlled and baseline values of arterial pressure, Pa_{CO_2}, Pa_{O_2} and CBF were obtained. CBF was determined by external scintillation counting following the intracarotid injection of xenon-133 in saline.

In the first instance, hypocapnia was induced (mean Pa_{CO_2} 30 mm Hg (SD 1)) and a measurement of CBF obtained. Subsequently, following the re-establishment of baseline values, the inspired oxygen concentration was decreased to produce arterial oxygen tensions of approximately 75, 55, 40 and 25 mm Hg. CBF was determined at each step decrease in oxygen tension.

At the conclusion of the investigation the brain of each animal was perfusion-fixed and a complete neuropathological examination undertaken.

Although hypocapnia produced decreases in CBF in four of the five animals the overall response (0.7 ml min^{-1} per 100 g per mm Hg) was significantly less than that found previously in similar animals without intracranial pathology.

The decreases in Pa_{O_2} resulted in increases in CBF (baseline value 57 ml min^{-1} per 100 g (SD 6)) such that at arterial oxygen tensions of approximately 75, 55 and 40 mm Hg values of cerebral blood flow were 73 (SD 6), 93 (SD 11) and 123 (SD 7) ml min^{-1} per 100 g respectively. (At Pa_{O_2} of approximately 25 mm Hg circulatory failure was encountered in three animals.) Thus, the pattern of the response to hypoxia observed in these animals with an artificial subarachnoid haemorrhage was quite different from that described in an intact preparation (McDowall, 1966).

The possible relevance of these observations to the management of patients will be considered.

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CONTROL OF INTRACRANIAL PRESSURE (ICP) DURING INTENSIVE CARE

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ICP is one of the basic indices influencing outcome of patients suffering from neurological disorders. During intensive care it is the aim to decrease rapidly an increased ICP and to prevent any pressure increase when there is danger of impaired cerebral perfusion. Long-term monitoring of ICP has become more and more widespread. We investigated the influence of some techniques used in anaesthesia and intensive care: hyperventilation, PNPV, PEEP, intubation, suctioning; and some sedatives, analgesics and diuretics. ICP was monitored in neurosurgical patients by use of a Gaeltec Ltd extradural transducer (ICT/b) or a ventricular catheter.

The results show that often some degree of increase in ICP occurs in association with intubation, PEEP or suctioning. It can be diminished or even abolished by the use of i.v. anaesthetics, sedatives, or changes in positioning of the patient's head. ICP is decreased rapidly by hyperventilation and to some degree by PNPV. The effect of hyperventilation does not last long, however. Diuretics such as mannitol decrease ICP. When the pre-existing ICP is very great (more than 40 mm Hg) often no reducing effect occurs. In this situation even barbiturates (thiopentone) in a high dose (150 mg h^{-1} after a bolus injection of 400 mg in adults) are to no avail. Continuous control of ICP plays an important role in monitoring today. A sudden pressure increase signals a complication such as bleeding or brain swelling, when other factors can be excluded. The pressure increase will often lead to further investigation such as computer tomography.

However, it is not just the magnitude of the pressure in mm Hg, but the shape of the recorded pressure which is of interest. The size of pulsations within the pressure curve give information about the existing compliance of the brain. In cases of cerebral death pulsations will diminish but not completely disappear, and autoregulation is lost.

TRIALS OF AUDIOTAPE-SLIDE TECHNIQUES IN TEACHING

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The effectiveness of audiotape-slide teaching can be assessed because each programme has a permanent record. Lectures, in contrast, are more difficult to assess as individual lectures lack this consistency.

Several teaching hospitals in Scotland have co-operated in trials to assess the effectiveness and the ideal format for a series of audiotape-slide materials prepared in Glasgow Royal Infirmary. Although the studies were designed for this media, they may be relevant to the planning of other teaching assessment trials. In the first two trials assessment was limited to two types of questionnaire.

An *interim questionnaire* monitors that the essential teaching points are being communicated. Every 5-10 min the programme stops so that the student can complete the questionnaire. Marking this questionnaire provides an indication of effectiveness of the teaching. Additional advantages of the questionnaire are that the active participation of the student in its completion reinforces the effectiveness of teaching and provides feedback. Furthermore, the completed questionnaire can act as a summary for the student.

After conclusion of the teaching course the student completes an *opinion questionnaire* to give his preferences as regards the modes of presentation of the programmes and his opinions comparing audiovisual presentation and other forms of teaching.

Anaesthetists in training readily co-operated in the completion of these questionnaires and so in the latest two trials additional *multiple choice questionnaires* (MCQs) have been introduced as follows:

A pre-test of 30 MCQs is completed before commencing study. This assesses the initial level of knowledge which is not checked by the interim questionnaire.

A similar test of 30 MCQs is used to assess the knowledge retained after completion of the course.

The first two trials (Parbrook and Parbrook, 1976; Parbrook, Parbrook and Boyle, 1977) compared the use of materials as a group and individually and compared synchronized and non-synchronized apparatus. The third trial (Parbrook, 1979) compared use with simple apparatus and that in a carrel and the most recent trial compared the effectiveness of audiotape and slides and script and slides.

In addition to these comparisons, the trials provide comparisons of the individual programmes and parts of them so that aspects requiring upgrading can be identified.

The opinions of the anaesthetists have indicated the acceptability of the audiovisual technique compared with other forms of teaching. As some of the programmes have already been translated, it is possible that co-operative trials with other European centres can be arranged.

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POSTER DEMONSTRATIONS

PLASMA CATECHOLAMINE CONCENTRATIONS AND HAEMODYNAMIC STUDIES DURING PHAEOCHROMOCYTOMA RESECTION

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Haemodynamic responses during surgery for phaeochromocytoma are caused by the pharmacological effects of excessive concentrations of circulating catecholamines. The present study was designed to correlate the haemodynamic responses with plasma catecholamine concentrations during surgical procedure.

Six patients (25-60 yr) undergoing excision of phaeochromocytoma have been studied. The patients were not treated with adrenergic blocking agents before operation. Premedication consisted of flunitrazepam and droperidol. Anaesthesia was induced with a combination of droperidol and phenoperidine, supplemented by diazepam. Neuromuscular block was achieved with pancuronium. Hypertensive crises were treated by infusion of phentolamine. Replacement of blood volume, which was begun at the start of operation, was accelerated during removal of the tumour. The set of measurements for plasma catecholamine concentration and haemodynamic data (PWP = pulmonary wedge pressure, MAP = mean arterial pressure, CI = cardiac index, SVR = systemic ventricular resistances) were made at the following times: before the induction of anaesthesia (t_0), after tracheal intubation (t_1), after skin incision (t_2), during abdominal exploration (t_3) and tumour handling (t_4), after resection (t_5) and after the end of anaesthesia (t_6).

The results (mean ± SEM) are shown in table I (p. 250P).

This study shows that hypertensive crises were caused by an increase in SVR caused by an increase in plasma catecholamine concentration. The maximal changes were observed during tumour handling, resulting in an increase in PWP and a decrease in CI. these haemodynamic changes reflect a transient left ventricular failure, reversed with interruption of handling of the tumour by the surgeon or by vasodilator therapy. The results of this study suggest that beta-blockers are contraindicated in these patients. Fluid should be replaced cautiously until tumour removal, because of the risk of congestive heart failure.

TABLE I. *NA = noradrenaline (normal range* <2 *nmol litre*$^{-1}$*); A = adrenaline (normal range* <0.5 *nmol litre*$^{-1}$*)*

	t_0	t_1	t_2	t_3	t_4	t_5	t_6
PWP (mm Hg)	10	11	11	12	20	11	10
	±2	±3	±2	±1	±3	±1	±2
MAP (mm Hg)	118	129	125	140	172	91	89
	±15	±11	±9	±10	±8	±3	±7
CI (m^{-2})	4.9	4.3	4.2	4.6	3.9	3.2	4.0
	±0.3	±0.4	±0.5	±0.5	±0.7	±0.4	±0.5
HR (beat min^{-1})	98	113	117	111	115	115	109
	±11	±9	±10	±10	±9	±10	±6
SVR (dyne s cm^{-5})	1180	1475	1505	1470	2405	1380	1075
	±150	±170	±175	±100	±375	±100	±85
NA (nmol $litre^{-1}$)	51	56	44	98	205	83	17
	±26	±19	±11	±40	±74	±33	±7
A (nmol $litre^{-1}$)	6	8	7	14	36	10	5
	±3	±2	±3	±3	±12	±2	±1

EFFECTS OF THIOPENTONE ON THE PULMONARY CIRCULATION

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In 12 normal unpremedicated subjects (seven women, five men) aged 15–40 yr (mean 25.6) the action of thiopentone 10 mg kg^{-1} on the pulmonary circulation was studied.

Before and after i.v. thiopentone, arterial blood P_{O_2}, P_{CO_2} and pH were measured and the following recorded: e.c.g., systemic arterial pressure, pulmonary artery pressure and cardiac output (thermodilution method).

After thiopentone arterial blood-gases and acid–base indices were not changed significantly.

Heart rate was increased ($P<0.01$), and systolic, diastolic and mean systemic arterial pressures, cardiac output and stroke volume decreased significantly ($P<0.001$), but the increase in systemic vascular resistance was not significant ($P<0.2$). Pulmonary artery systolic pressure and pulmonary vascular resistance decreased significantly ($P<0.01$). Diastolic and mean pulmonary artery pressures decreased markedly ($P<0.001$).

I.v. thiopentone has a distinct action on the pulmonary circulation. After thiopentone injection both pulmonary arterial pressure and total pulmonary vascular resistance decreased significantly. The decrease in TPVR was partly a result of the decrease in cardiac output but it may be that the diminution in pulmonary vascular tone contributes to this result.

OBSTETRIC ANALGESIA WITH FENTANYL–BUPIVACAINE BY THE EXTRADURAL ROUTE

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We report on the application of a combination of 0.375% bupivacaine 8 ml and fentanyl 2 ml. Thirty healthy pregnant women at term, aged 14–35 yr (mean 23.1, SD ±4.29), weight 50–80 kg (mean 68.67, SD ±7.45), were treated in the course of labour. We selected a dose of 0.1 ml/kg body weight (bupivacaine 0.0003 mg and fentanyl 0.001 mg) given through an extradural catheter placed 3 cm below the point of insertion at L1–L2. The first dose ranged from 5 to 8 ml (mean 6.93, SD ±0.77). The latency interval varied from 2.5 to 4 min (mean 3.28, SD ±0.47) and the duration of effective analgesia was 150–60 min (mean 105.83, SD ±29.77). Eighteen of our 30 patients required a second dose and five required a third dose, similar to the first.

Additional 0.5% bupivacaine given through the catheter was used for seven patients undergoing forceps delivery, and six undergoing Caesarean section; doses were (respectively) mean 6.86 ml, SD ±0.90; mean 10.33 ml, SD ±1.97.

Our results were highly satisfactory. No evidence of fetal or neonatal depression was noted in any infant (20 females and 10 males; weight 2400–4480 g, mean 3318, SD ±476.44).

We present the data of this series with particular reference to cardiocirculatory, ventilatory and acid–base indices, and compare the results with our own earlier experience with extradural fentanyl alone, presented last year.

ETODOLAC IN POSTOPERATIVE PAIN: A DOUBLE-BLIND STUDY WITH ASPIRIN AND PLACEBO

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A study was conducted to compare the analgesic activity of single oral doses of Etodolac (a new non-steroid anti-inflammatory drug with analgesic activity) 25, 50, 100, 200 and 400 mg with aspirin 650 mg and placebo. One hundred and forty-six patients with moderate or severe pain recovering from orthopaedic or urological procedures received one of the test drugs 24 h after operation according to a randomized allocation balanced as to initial pain intensity. Data for pain intensity and pain relief, from which efficacy parameters were determined, were collected at 30 min, then hourly for 8 h.

Vital signs and adverse reactions were recorded. One hundred and forty-two patients completed the study. The average response to Etodolac 100, 200 and 400 mg was superior to placebo. On the basis of SPID (sum of pain intensity differences), TOTPAR (sum of pain relief scores) and duration of analgesia, Etodolac 400 mg was also superior to aspirin 650 mg. Mild and moderate side-effects possibly related to Etodolac were reported in 4/146 patients (2.7%). This study provides evidence that Etodolac in doses of 100 mg and greater is an effective and well tolerated analgesic.

PLASMA AND CEREBROSPINAL FLUID AMINO ACID DISTRIBUTION RATIOS IN HYPERCAPNIA

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A comparative study of the plasma and cerebrospinal fluid amino acid distribution ratios between patients in acute respiratory failure (ARF) (20 subjects) and in hypercapnic coma (22 subjects) has been made.

The analysis of data was according to the Spackman, Stein and Moore method with a 3A-29 Aminoacid Autoanalyzer (C. Erba Ltd, Milan). The results (table I) were: methionine, phenylalanine, leucine, lysine, valine, tyrosine, histidine, arginine, taurine and glycine distribution ratios were reduced compared with control, particularly in hypercapnic coma. In hypercapnic coma there was a change in the pool of free amino acids in plasma and cerebrospinal fluid and the distribution of phenylalanine and tyrosine between plasma and cerebrospinal fluid appears to indicate that the brain uptake mechanisms of these compounds are dependent on the enzymic inhibition of catecholamine synthesis and alterations of active transport across the cerebral membrane.

Table I. *Plasma c.s.f. amino acid distribution ratios*

	Blanks	Hyp. coma	ARF
Essential			
Methionine	8.5	2.4	7.3
Phenylalanine	6.8	3.2	5.3
Iso-leucine	12.2	11.4	10.3
Threonine	7.3	2.5	3.9
Leucine	10.8	5.7	8.4
Lysine	6.0	4.0	8.4
Valine	11.7	7.7	11.5
Semi-essential			
Tyrosine	7.7	1.6	5.5
Hystidine	6.3	3.7	5.1
Arginine	4.9	1.6	1.9
Non-essential			
α-Amino butyric	10.5	16.5	6.2
Taurine	7.2	0.5	—
Glutamic acid	4.2	—	2.6
Ornithine	8.7	7.0	20.2
Glycine	29.7	7.4	13.6

JAUNDICE AND ANAESTHESIA

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The presentation deals with anaesthetic problems occurring during surgery for obstructive jaundice caused by either benign or malignant disease. It is based on studies of the literature, on personal experience and on the results of an inquiry in 207 anaesthetic departments in Austria, Switzerland and the Federal Republic of Germany. One hundred and eighty-seven of 207 responded.

The anaesthetist must avoid causing additional impairment of the liver function while preparing the patient for operation, in prescribing premedication and during anaesthesia. Neuroleptanalgesia is the most commonly used method of anaesthesia. Halothane is little used, less for medical reasons than to avoid legal or forensic consequences. Regional anaesthesia (spinal or extradural anaesthesia) was never used exclusively in operations for obstructive jaundice but was often combined with general anaesthesia. Extradural nerve block via a catheter offers the additional advantage of postoperative analgesia. The determining factor in anaesthetic management is the presence of hepatic insufficiency, which also determines the use of parenteral nutrition.

RADIOCARDIOGRAPHY IN THE INTENSIVE CARE UNIT: PRELIMINARY REPORT

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As a non-invasive method of haemodynamic monitoring radiocardiography (RCG) correlates well with invasive methods. We have examined 25 patients during and after mechanical ventilation for the treatment of various types of respiratory insufficiency. The bedside mobile RCG set was used in the Intensive Care Clinic of our Institute. As a marker, indium was injected to the subclavian vein. The RCG recording was obtained using a scintillation camera, placed above the precordial area of the patient's chest, and coupled to the e.c.g. For haemodynamic evaluation we measured blood volume, cardiac output, stroke volume, pulmonary transit time and pulmonary blood volume. The preliminary results of the studies performed are encouraging and in our opinion radiocardiography can serve as a non-invasive and useful tool.

ANALYSIS OF 130 000 ANAESTHETICS AT THE CENTRE HOSPITALIER UNIVERSITAIRE, NANCY

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More than 130 000 anaesthetics have been given over 5 years at the Centre Hospitalier Universitaire of Nancy. Eighty-column punch cards were used to store the essential data.

Examples to illustrate the advantage of this method will be presented:

Analysis of operative morbidity and mortality (1.2% of cases) and statistical analysis of risk factors;

Study of the clinical work of groups or departments permitting, from precise data, a better service and improved training opportunities in anaesthesia and resuscitation.

The work and cost involved are repaid by a better understanding of research opportunities, improved teaching and more efficient management.

PHARMACOKINETICS OF FENTANYL IN CHILDREN

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The pharmacokinetics of fentanyl were studied in seven male children aged 4–7 yr, undergoing a minor surgical operation.

A single i.v. injection of 3 mg kg^{-1} was given after induction of anaesthesia with enflurane. Anaesthesia was maintained with enflurane after injection of norallyl-toxoferine 0.2 mg kg^{-1} and endotracheal intubation. The lungs were ventilated mechanically with 50% nitrous oxide in oxygen.

A plastic cannula was inserted in a forearm vein and blood samples were taken (with the parents' permission) during the 24-h period following the fentanyl injection. A total of 16 samples of 5 ml each were taken.

The fentanyl content of each sample was determined by radioimmunoassay. The results were plotted on semi-logarithmic paper.

The results showed that fentanyl, in this group of children, had a half-life substantially longer than in adults. We found a half-life of 6–8 h in the seven children studied. The difference could be related to the greater amount of fat in the body structure of young children.

E.E.G. ANALYSIS AND CLINICAL EFFECTS OF LEVONANTRADOL IN HUMAN VOLUNTEERS

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Levonantradol, a cannabis derivative, has been found to be effective against nausea and vomiting. It is presently under study as an analgesic.

We administered levonantradol 20 $\mu g\ kg^{-1}$ i.m. to volunteers of both sexes, aged 18–68 yr, in a double-blind controlled trial. Distilled water was used as placebo.

A sedative effect was observed in eight of 10 subjects given levonantradol. Alteration of mood and perception were described by several subjects, in one case reaching a typical psychedelic experience.

E.e.g. was recorded from the dominant hemisphere via frontal–rolandic and occipital–rolandic needle electrodes. Recordings lasted 30 min with 1-h intervals between recordings. Both a conventional e.e.g. and Berg-Fourier recordings were made.

The observed modifications were alpha rhythm while reading, disappearance of the "réaction d'arrêt" when opening the eyes, and disappearance of antero–posterior differentiation. These alterations can be considered as characterizing a somnolence, different from any physiological state. There was an increase in the 6–14 Hz spectrum.

These alterations in the anterior areas could be related to a specific action on the limbic system.

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ERWIN RIESCH SYMPOSIUM

CONTROLLED HYPOTENSION IN NEUROANAESTHESIA

Tubingen September 27–30, 1981

SESSION I

PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS

Chairmen: J. E. Cottrell and K. Huse

DRUGS USED FOR INDUCED HYPOTENSION

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Drugs which may be used to induce hypotension during anaesthesia for neurological surgery include: general anaesthetic agents, α-adrenergic receptor blockers, β-adrenergic receptor blockers, autonomic ganglion blockers, direct acting vasodilators, and those used to induce spinal or extradural analgesia.

General anaesthetic agents, particularly halothane, produce hypotension by direct actions on the vasomotor centre, the myocardium and the peripheral resistance. Their effects are potentiated by IPPV, particularly if tubocurarine is used also. Until recently, autonomic ganglion blockade was a popular technique in the United Kingdom, the decreases in pre- and after-load leading to decreases in cardiac output and peripheral resistance. This technique has been replaced largely by agents, such as sodium nitroprusside, which act directly on resistance vessels, there being little change in cardiac output. Although early reports of toxicity from an overdose of this agent caused some concern, more rational use of the drug has largely eliminated these fears. Most recently a combined α- and β-receptor blocker (labetalol) has been used during neurosurgery. This drug is certainly effective, but is not without certain disadvantages.

SPECIFIC VASCULAR MECHANISMS OF HYPOTENSIVE AGENTS

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Contraction of the smooth muscle cells within the vessel wall is, to a certain extent, the prerequisite for vasodilatation. The contractile process is triggered either by a mechanism within the membrane itself, or by the binding of vasoactive molecules to the membrane. An influx of extracellular Ca^{2+} into the cell or a release of Ca^{2+} from intracellular stores, or both, then occurs. As a result, the intracellular concentration of activator Ca^{2+} necessary for the interaction between the actin and myosin filaments increases.

Vasodilating drugs decrease the amount of activator Ca^{2+} available. This can be achieved in two ways which may be designated broadly as inhibition of vasoconstriction and direct vasodilatation (Van Nueten and Wellens, 1979). Inhibitors of vasoconstriction decrease the release of endogenous vasoconstrictors, or affect their binding to receptors on the membrane. Drugs in this group are: ganglion blocking agents such as trimetaphan; inhibitors of adrenergic transmission which block the release of noradrenaline from adrenergic nerve terminals—halothane probably acts by this mechanism; alpha-adrenoceptor blocking drugs such as phentolamine and prazosin; drugs affecting the action of angiotensin which can be inhibited by blockade of the converting enzyme (captopril) or by occupation of the angiotensin receptor site (saralasin).

So-called direct-acting vasodilators decrease the influx of extracellular Ca^{2+} across the cell membrane, or the availability of intracellular Ca^{2+}. The former mechanism applies to calcium antagonists (verapamil, nifedipine, flunarizine, cinnarizine), the latter to various different types of drugs. Beta-adrenoceptor agonists—possibly by activating adenylate cyclase—as well as inhibitors of phosphodiesterase such as theophylline and papaverine, enhance the removal of activator Ca^{2+} by increasing the intracellular c-AMP concentration. Nitroglycerine (NTG) and sodium nitroprusside (SNP) appear to exert their relaxing effects on vascular smooth muscles by interfering with the intracellular activation of Ca^{2+}. The exact mechanism of this action has, however, yet to be investigated. The influx of calcium-45 into the cell, and its uptake by subcellular fractions, are only slightly inhibited by NTG, and are not influenced by SNP at all (Thorens and Haeusler, 1979). The involvement of SH-groups located within the cell membrane or intracellularly, in the action of vasodilators (Needleman et al., 1973) is also being considered.

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REBOUND ARTERIAL HYPERTENSION FOLLOWING DISCONTINUATION OF SODIUM NITROPRUSSIDE

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Rebound hypertension following discontinuation of nitroprusside (NP) can be hazardous, especially in patients with heart disease or after clipping of cerebral aneurysms. Plasma renin activity (PRA), plasma catecholamine concentrations and systemic haemodynamics were examined in 16 patients before, during and after discontinuation of NP. Ten patients (group 1) received NP only, and six patients received NP and propranolol i.v. (group 2). In group 1, PRA and catecholamine concentrations increased significantly with infusion of NP. The decrease in arterial pressure was associated with a decrease in systemic vascular resistance (SVR) and an increase in cardiac output ($P < 0.01$). Following discontinuation of NP, PRA and catecholamine concentrations were still significantly increased. Arterial pressure and SVR increased, whereas CO decreased. In group 2, the increases in PRA and plasma catecholamine concentrations were significantly less than in group 1. Furthermore, there were no significant changes in the concentrations of these vasoactive substances or in haemodynamics after the discontinuation of NP. In conclusion, rebound hypertension observed following discontinuation of NP is probably related to increases in PRA and the concentrations of the catecholamines and can be attenuated or prevented by pretreatment with propranolol.

THE PLACE OF VOLATILE ANAESTHETICS DURING INDUCED HYPOTENSION IN NEUROSURGICAL PATIENTS

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Arterial pressure is decreased during neurological surgery to: decrease the risk of rupture of a cerebral aneurysm, decrease blood loss and decrease brain swelling and intracranial pressure in those situations in which autoregulation is impaired. The agents used are "hypotensive" drugs and certain anaesthetic agents. Among the latter, volatile anaesthetics such as halothane and enflurane play a part by aiding the control of hypotension so that the decreases in arterial pressure will be gradual and critical cardiovascular situations will not arise.

During use of "hypotensive" drugs arterial pressure will often decrease steeply and intracranial pressure will change unexpectedly as demonstrated by our results. Cerebral vessels dilate under halothane and enflurane and this may protect against postoperative spasm in patients with an aneurysm. Moreover, halogenated anaesthetics counteract some of the endocrinological side-effects of the specific hypotensive drugs. They decrease the activation of the renin–angiotensin system and of the sympathetic nervous system. In most clinical situations the negative effect of halothane and enflurane on cardiac contractility can be neglected, but their effects on intracranial pressure must be taken into consideration.

In clinical practice halothane, or enflurane, and a direct-acting hypotensive drug will be used in combination, especially during intracranial surgery for aneurysms.

INTERACTIONS OF ANAESTHETIC DRUGS AND NEUROMUSCULAR BLOCKING DRUGS WITH THOSE DRUGS COMMONLY USED FOR CONTROLLED HYPOTENSION

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Drug interactions can occur *in vitro* ("drug interference") and *in vivo*. The mechanisms discussed in the present paper involve interactions occurring *in vivo* under the conditions of controlled hypotension and anaesthesia.

Pharmacokinetic interactions may be caused by decreases in cardiac output, changes of organ perfusion, inhibition of degradation or renal excretion, or alterations in protein binding. Changes in organ perfusion during controlled hypotension result in lower concentrations of drugs such as benzodiazepines, fentanyl and barbiturates in the c.n.s.; whereas the disposition in muscles and fat is enhanced. Thus, larger doses of these drugs are necessary. The degradation of suxamethonium is inhibited by trimetaphan (Sklar and Lanks, 1977), and thus the half-life of suxamethonium is prolonged under trimetaphan-induced hypotension. Renal excretion of neuromuscular blockers is impaired by deep hypotension and concomitantly decreased renal perfusion. This is more likely to occur under trimetaphan hypotension than under nitroprusside (Wang, Liu and Kth, 1977).

Pharmacodynamic interactions are utilized in controlled hypotension in which inhalation anaesthetics, which decrease cardiac output, are used as part of the technique. Since nitroprusside-induced hypotension results in tachycardia as a result of sympathetic stimulation by the baroreceptor response, the effect of halothane on heart rate is desirable. Halothane-induced bradycardia is more pronounced, however, when using ganglioplegic agents. In contrast to nitroprusside, trimetaphan and nitroglycerine both augment the effect of neuromuscular blockers at the motor end-plate.

Nitrous oxide and nitroprusside have been demonstrated to decrease the body content of vitamin B12. Whereas nitrous oxide exerts its effect only following prolonged administration, the clinical administration of nitroprusside affects vitamin B12 concentration (Fahmy, 1981). An additive effect of both drugs is conceivable.

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SESSION II

CEREBRAL BLOOD FLOW AND METABOLISM UNDER CONDITIONS OF SYSTEMIC HYPOTENSION

Chairmen: L. Symon and K. Wiedemann

AUTOREGULATION OF CEREBRAL BLOOD FLOW: EFFECTS OF HYPOTENSIVE DRUGS

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The relationship between cerebral blood flow and the pressure perfusing the brain is of paramount importance in situations as diverse as hypovolaemic shock, controlled or inadvertent hypotension during anaesthesia and surgery, and situations in which intracranial pressure is increased. Early studies demonstrated the remarkable stability of the blood flow to the brain despite *moderate* variations in perfusion pressure, and the phenomenon of autoregulation was characterized. More recent investigations delineated those values of mean arterial pressure beyond which the autoregulation of the cerebral circulation was ineffective and the basic pattern of the pressure/flow relationship was established.

The rational application of the technique of induced hypotension to neurological surgery depends on an appreciation of those alterations to the basic pattern of the relationship brought about by the administration of appropriate hypotensive agents and by the presence of intracranial pathology. Therefore, it is pertinent to consider some of these alterations in more detail.

In the intact animal, Fitch and colleagues (1976) demonstrated that the pressure/flow plateau was extended to lower values of mean arterial pressure, when drug-induced hypotension was compared with hypotension as a result of haemorrhage. The drugs studied were trimetaphan plus halothane, nitroprusside plus halothane and halothane alone, and it was argued that not only did blood flow remain stable, but autoregulation persisted to significantly lower values of mean arterial pressure. However, further investigations in which hypotension was induced with nitroprusside alone (Pickard et al., 1981) or by nitroglycerine (unpublished observations) would suggest that, even in the animal without intracranial pathology, autoregulation was affected by the pharmacological actions of these hypotensive agents (increases in flow were demonstrated with both drugs). If one accepts also the earlier observations of Stoyka and Schutz (1975), that animals given trimetaphan alone showed no evidence of autoregulation (blood flow decreased), it could be contended that each of the types of drug commonly used clinically to induce hypotension acts differently on the cerebral circulation.

This may be so, but it seems more likely that, during pharmacologically-induced hypotension, the effect on the cerebral circulation is the result of competition between direct cerebral vasodilatation, decreases in perfusion pressure and possible impairment of autoregulation. Under these conditions the concomitant responses of the peripheral circulation and the myocardium may be appropriate considerations.

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DELIBERATE HYPOTENSION—PHARMACOLOGY AND CLINICAL MANAGEMENT

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Hypotension is induced to facilitate surgery by creating a relatively bloodless field, thereby decreasing operative time and the need for blood transfusion. Surgical procedures which benefit from induced hypotension include the clipping of cerebral aneurysms, the repair of arteriovenous malformations and the resection of vascular tumours. In addition, perioperative hypertension frequently requires treatment to prevent myocardial infarction and the formation of cerebral oedema.

Hypotension is commonly induced pharmacologically with halothane, sodium nitroprusside (SNP), trimethaphan, nitroglycerine (NTG) and, recently, phentolamine. Mechanical manoeuvres such as positive airway pressure or changes in position are added as fine adjustment. Combination of these agents and manoeuvres may have advantages. Halothane decreases the dosage of SNP and facilitates NTG-induced hypotension. Some investigators have advocated the use of beta-blocking drugs in conjunction with these hypotensive drugs.

Monitoring should consist of precordial e.c.g. with a V_1 recording, arterial pressure, a temperature probe, oesophageal stethoscope, urinary bladder catheter, and central venous pressure or balloon-tipped flow directed pulmonary artery catheter. Neurophysiological monitoring is obtained using the electroencephalograph (e.e.g.), evoked potentials (EP), or the cerebral function monitor.

Complications from induced hypotension are related to the patient's physical status, the hypotensive agent or technique used, and the degree of hypotension induced.

Ischaemic complications occur more commonly in patients with pre-existing ischaemic vascular disease. Specialized monitoring (e.e.g., EP, and e.c.g.) will detect early cerebral or myocardial ischaemia.

Hazards of hypotensive drugs include a lack of control, direct toxicity or evidence of toxic metabolites, alterations in major organ autoregulation and hormonal balance. Halothane metabolism can produce toxic metabolites, especially in the presence of enzyme inducers and low oxygen content. Alterations in major organ blood flow occur after halothane administration. SNP may produce cyanide toxicity (>1 mg kg^{-1} acutely), rebound hypertension from increased plasma renin activity (PRA), increases in intracranial pressure (i.c.p.) and cerebrospinal fluid cyanide concentration, interference with platelet aggregation and concentration, hypothyroidism after prolonged administration, and thiocyanate toxicity if renal failure exists. NTG increases i.c.p. and certain patients are refractory to its hypotensive action. Trimetaphan blocks autonomic ganglia and produces unwanted gastrointestinal, genitourinary, and pupillary effects. Tachyphylaxis occurs frequently. Phentolamine produces hypotension by alpha-adrenergic blockade and a direct c.n.s. effect. ICP is unaffected. In healthy man hypotension can be induced to mean arterial pressure (m.a.p.) 50 mm Hg: hypertensive patients require greater pressures. Hyperventilation (4 kPa) should be avoided during deliberate hypotension to m.a.p. of 50 mm Hg. Inadequate tissue perfusion can be detected by monitoring arterial blood–gas tensions or changes in mixed venous oxygenation.

Anaesthetic agents which suppress cerebral oxygen demand will allow induction of m.a.p. <50 mm Hg, but appropriate monitoring (cerebral metabolites, pyruvate/lactate) is required.

HYPERGLYCEMIA, TISSUE LACTIC ACIDOSIS AND ISCHAEMIC BRAIN INJURY

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Interest is directed currently towards the role of severe tissue lactic acidosis as a pathogenic factor in the development of irreversible brain cell damage in situations with a critically reduced cerebral perfusion pressure. Thus Myers and co-workers (Myers, 1979) observed that the nutritional state of experimental animals influenced the outcome of induced brain ischaemia and suggested that failure of recovery was related to excessive accumulation of lactate in the brain.

When the oxygen supply to the tissue is decreased below the critical value for oxidative metabolism, impaired ATP production leads to cerebral energy failure and ionic shifts with loss of cellular K^+ and an increase in intracellular Na^+ concentration. Since these events occur within a few (2–4) minutes (that is, within a time period that is compatible with full neurological restitution), their exact relationship to irreversible damage is uncertain. However, cellular lack of oxygen will also lead to extensive decreases in pyridine nucleotides (NAD^+) and other redox couples. The intracellular redox change strongly favours pyruvate reduction in the lactate dehydrogenase equilibrium which leads secondarily to lactic acid production from available carbohydrate substrate. If cerebral blood flow (c.b.f.) is totally interrupted (complete ischaemia) lactate accumulates to a value determined by the preischaemic tissue stores of glucose (and glycogen). On the other hand, if c.b.f. is not totally abolished (incomplete ischaemia), some glucose is transported to the brain with the residual blood flow and continued anaerobic glycolysis exaggerates tissue lactic acidosis, which may become excessive.

Several experimental studies have shown that certain types of incomplete ischaemia may be more harmful than complete ischaemia (Rehncrona, Rosén and Siesjö, 1981) and the question arose as to whether this difference in outcome was related to the lactic acidosis. The amount to which lactate accumulates in the incomplete ischaemic brain will depend on: (1) the rate of the residual blood flow, (2) the duration of ischaemia and (3) the blood glucose concentration. We recently studied the role of brain lactic acidosis in the development of irreversible cell damage in severe incomplete ischaemia (c.b.f. about 5% of normal) in artificially (nitrous oxide in oxygen) ventilated rats (Rehncrona, Rosén and Siesjö, 1980, 1981). Brain ischaemia was induced by hypovolaemic hypotension combined with bilateral carotid artery clamping. After a 30-min ischaemic period cerebral perfusion pressure was restored by removing the artery clamps and restoring the arterial pressure. Recovery was evaluated by metabolic and neurophysiological indices and the degree of morphological damage evaluated by light and electron microscopy (H. Kalimo, this symposium). All animals were fasted before the experiment and the accumulation of lactate in the brain during ischaemia was varied by giving an infusion of either a physiological saline solution (blood glucose 5–6 μmol ml^{-1}) or a glucose-containing solution (blood glucose 25–35 μmol g^{-1}) i.v. just before ischaemia. In food-deprived animals not receiving glucose, tissue lactate concentration increased to about 15 μmol g^{-1}. Upon recirculation these animals showed considerable recovery of cerebral energy metabolism, return of spontaneous electrocortical activity and of cortical responses to somatosensory stimulation. Microscopy failed to show widespread or irreversible damage (H. Kalimo, this symposium). Animals with hyperglycaemia, induced after the ischaemia (separate animals) showed similar recovery. However, in animals rendered hyperglycaemic before ischaemia, brain lactate increased to more than 30 μmol g^{-1} and these animals did not recover in any of the indices studied, indicating irreversible brain damage. It is concluded that the degree of tissue lactic acidosis is critical for postischaemic recovery and that severe hyperglycaemia should be avoided in clinical situations with a pronounced reduction in cerebral perfusion pressure. Since the deleterious effect of excessive lactate accumulation most probably can be attributed to a severe decrease in intracellular pH, search for buffers efficient in the intracellular compartment of the brain is warranted.

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INTERACTION BETWEEN BLOOD GLUCOSE CONCENTRATION, DEGREE OF CEREBRAL TISSUE ACIDOSIS AND CELLULAR K+ RELEASE UNDER CONDITIONS OF CRITICAL CORTICAL BLOOD FLOW

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Substantial evidence indicates that the clinical outcome of patients and animals with severe disturbances of cerebral blood flow (c.b.f.) is dependent on the preischaemic blood glucose concentration (Myers and Yamaguchi, 1977; Pulsinelli et al., 1980). For the anaesthetist this may be of significance during deliberate hypotension in patients suffering from disturbances of glucose metabolism. The present investigation was performed to determine whether this correlation was reflected in the severity of the derangement of cerebral extracellular ionic equilibrium.

Experiments were performed on 12 cats under general anaesthesia and artificial ventilation. Mean arterial pressure (m.a.p.) and end-expiratory carbon dioxide concentration were recorded continously. Cerebral extracellular H^+ and K^+ activities were measured with ion-selective microelectrodes implanted, via a cranial window, 500 μm into the cortical area supplied by the A. cerebri media (MCA) (Heuser, 1981). Critical levels of regional perfusion were established by reversible clipping MCA or its cortical branches via a lateral approach. In all animals clipping was performed three times, each of 10 min. The second and third clippings were not undertaken until extracellular ionic equilibrium had been reattained. Before the second and third clippings, glucose was administered i.v. in order to vary the preischaemic blood glucose concentration between 5 and 25 mmol litre^{-1}. In three cats, clamping was performed without glucose administration. During critically reduced c.b.f., different levels of hyperglycaemia resulted in decreases in tissue pH of 0.6–1.4 pH unit; the decrease in hypoglycaemia was less pronounced. Extracellular K^+ concentration increased to peak values of 70 mmol litre^{-1}, thus indicating anoxic cell depolarization. However, any significant sign of altered membrane stability during hyperglycaemia was not detected. Extracellular clearance of K^+ was usually much more rapid than that of H^+. We conclude that tissue acidosis may contribute to the severity of neurological deficits during critically reduced c.b.f., thus requiring us to establish normal blood glucose concentrations in patients before induction of hypotension, especially when very low values of arterial pressure are desired.

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COMPARISON OF CHANGES IN E.C.F. POTASSIUM CONCENTRATION AND pH OF THE BRAIN BETWEEN TRIMETAPHAN- AND NITROPRUSSIDE-INDUCED HYPOTENSION

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Hypotensive techniques are frequently used during neuroanaesthesia to improve operating conditions, infusions of sodium nitroprusside (NTP) or trimetaphan (TMP) i.v. being used most commonly. NTP and TMP differ significantly in their effects on the cerebral circulation (Michenfelder and Theye, 1977; Maekawa, McDowall and Okuda, 1979). This study attempts to demonstrate the derangements in cerebral extracellular fluid (e.c.f.) ion homeostasis which accompany the circulatory change produced by these agents in an animal model using ion-selective microelectrodes.

Thirteen cats, anaesthetized with nitrous oxide in oxygen and halothane, were ventilated to maintain normocapnia. Neuromuscular blockade was induced with pancuronium. Femoral vessels were cannulated for the measurement of mean arterial pressure (m.a.p.), the administration of i.v. fluids (Ringer's lactate 5 ml $kg^{-1} h^{-1}$) and the infusion of drugs. Bilateral burr holes were made over the parietal cortex and regional cerebral blood flow (rCBF) was measured over one cortex by krypton-85 clearance (ipsilateral intracarotid injection of krypton-85 via retrograde lingual artery cannula). Cortical e.c.f. potassium ion activity (K^+) and pH were measured in the contralateral cortex with implanted microelectrodes, of tip diameter less than 10 μm, at a depth of approximately 500 μm. For technical reasons K^+ measurements were made in 12 experiments and pH in eight experiments.

Following control measurements, m.a.p. was decreased by 5 mm Hg min^{-1} to 30–32 mm Hg, maintained there for 30 min and then decreased to 26–28 mm Hg for a further 15 min. Hypotension was induced with an i.v. infusion of either NTP (seven animals, maximum total dose 1 mg kg^{-1}) or TMP (six animals, maximum total dose 10 mg kg^{-1}). In addition, all animals received practolol 0.3 mg kg^{-1} i.v. Fine control of m.a.p. was achieved by the withdrawal of blood from the aorta and similar mean volumes were withdrawn in both groups. Statistical differences between means were assessed using either the Student *t* test or the Wilcoxon Rank Sum Test, as appropriate.

An acidosis developed in all the experiments. In the TMP group mean pH decreased from 7.21±0.05 unit to 5.85±0.15 unit during hypotension; the corresponding figures for NTP were 7.16±0.02 unit to 6.55±0.18 unit. Other results are presented in table I.

TABLE I. *Mean values ± SEM for m.a.p., rCBF, Pa_{CO_2} and K^+. *Significant difference between NTP and TMP mean values ($P<0.05$)*

	MAP (mm Hg)	rCBF (ml min^{-1} per 100 g)	Pa_{CO_2} (kPa)	Brain e.c.f. K^+ (mmol)
Control				
NTP	116±8	67±5	4.4±0.2	3.3±0.3
TMP	104±5	66±6	4.4±0.2	3.3±0.3
Hypotension				
NTP	27±0.3	53±10*	4.1±0.2	4.6±0.7*
TMP	28±1.0	16±5*	5.0±0.2	26.4±5.8*

Hypotension with TMP to the levels described produces cortical ischaemia sufficient to impair the ability of the neuronal cell membrane to maintain integrity with regard to potassium ions. An rCBF threshold for K^+ release into the cortical e.c.f. has been described by Astrup and colleagues (1977) and is supported by our data, although the absolute value of the threshold we observed is somewhat greater.

The cortical acidosis seen during TMP hypotension is readily explained by ischaemia, with accumulation of both lactate and carbon dioxide, but the similar acidosis noted with NTP in the presence of an adequate rCBF is more difficult to explain. If the human circulation behaves similarly, these results would suggest that NTP has advantages over TMP when profound hypotension is required during neurosurgery.

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METHODS OF CEREBRAL MEMBRANE STABILIZATION UNDER CONDITIONS OF CRITICAL BLOOD FLOW

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In the brain blood flow can be termed critical when the supply of oxygen becomes insufficient to support those cell functions, such as synaptic transmission, Na^+–K^+ pumping, and other tissue processes, which require energy. To protect the brain it is desirable to match a low flow state with a state of decreased metabolism so that a safe balance between oxygen supply and demand can be maintained.

The energy requiring cell functions in the brain can be inhibited one by one by specific drugs and, diffusely, by hypothermia. The barbiturates provide inhibition of synaptic transmission and associated oxygen and glucose consumption. Lignocaine in large doses has a similar "barbiturate-like" effect on synaptic transmission, and a specific "stabilizing" action on the membranes in the cerebral cortex caused by a Na^+-channel block similar to its local anaesthetic action on peripheral nerves. Consequently, lignocaine inhibits cerebral metabolism below the hitherto described barbiturate minimum by restricting the Na^+–K^+ leak fluxes and decreasing the load on the ion transport. Data so far obtained indicate that oxidative metabolism in the halothane-anaesthetized brain can be decreased to about 70% by barbiturates, to about 60% by lignocaine, but to about 20% by deep hypothermia (18 °C).

BLOOD FLOW AND OXIDATIVE METABOLISM OF THE YOUNG ADULT AND AGEING BRAIN

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The oxidative metabolism of the healthy adult brain is characterized by a balance between oxygen and glucose consumption. This balance is sustained during moderate changes in cerebral perfusion pressure and Pa_{CO_2}, the main factors controlling cerebral blood flow. It is well documented that both the autoregulation of cerebral blood flow and the responsiveness of cerebral blood vessels to carbon dioxide are maintained within certain limits in young adult brains. However, significant variations are found in the concentrations of some compounds of the glycolytic pathway in cortical grey matter under the conditions mentioned. These variations indicate an activation or an inhibition of glycolytic flux respectively.

In mentally and physically normal elderly subjects, the cerebral metabolic rates of both oxygen and glucose are decreased slightly. In experimental animals, there is an overall decrease in brain glucose concentration with ageing and an inhomogenous decrease in glucose utilization in the auditory and visual areas. There are, however, conflicting reports on whether cerebral blood flow is decreased with advancing age. The question as to whether autoregulation of cerebral blood flow or carbon dioxide reactivity of the cerebral vessels are unchanged or disturbed in normal cerebral ageing is far from being resolved. Early results on the effect of arterial hypoxaemia on cerebral cortical metabolism revealed more pronounced variations in oxidative glucose metabolism in 2-yr-old rats compared with 1-yr-old controls (the age of 1 yr in the rat corresponds to about 30 yr in man).

SESSION III

CEREBRAL ELECTRICAL ACTIVITY DURING SYSTEMIC HYPOTENSION IN NEUROANAESTHESIA

Chairmen: D. G. McDowall and G. Cunitz

THE USE OF EVOKED POTENTIALS AS A FUNCTIONAL MONITOR IN NEUROLOGICAL SURGERY WITH PARTICULAR REFERENCE TO SUBARACHNOID HAEMORRHAGE AND POSTERIOR FOSSA TUMOURS

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Changes in the brain's electrical activity have been related to critical decreases in cerebral blood flow in man and primates (Boysen, Engell and Trojaberg, 1977; Branston and Symon, 1980). Using transorbital middle cerebral artery occlusion to produce an acute ischaemic stroke in baboons, we have demonstrated a threshold relationship between impulse conduction in the c.n.s. and regional cerebral blood flow. In the acute phase, central conduction remains unchanged until c.b.f. decreases to less than 15 ml min^{-1} per 100 g (Hargadine, Branston and Symon, 1980) and, thereafter, is rapidly prolonged. These demonstrations stimulated the analysis of the roles of evoked potentials in clinical use. After median nerve stimulation we analysed the interpeak latency change between the negative peak recorded over the second cervical spinous process (N14) and the negative peak recorded over the scalp corresponding to the contralateral somatosensory cortex (N20) (Hume and Cant, 1978). Between these two major negative peaks a small positive deflux can be recorded (P15). It is generally agreed that N14 represents the arrival of the post-synaptic afferent volley at a fixed generator site, probably the dorsal column nuclei, and N20 represents the arrival of the impulse at the cortex. The N14–N20 interpeak latency is defined as Central Conduction Time (CCT), which is independent of a lesion below C2 and may represent genuine conduction time in the main. The origin of P15 is not clear, probably in the brain stem (Gott et al., 1977; Jones, 1977), although our work suggests the possibility of a thalamic origin.

CCT has a low standard deviation in normal subjects, and in patients with subarachnoid haemorrhage without clinical signs (5.4 ± 0.4 ms). Significant prolongation has been taken as 6.4 ms (mean + 2.5 SD) or longer.

In more than 70 patients with subarachnoid haemorrhage from radiologically shown aneurysm, we found that CCT was prolonged progressively with deterioration in the clinical grading (Hunt and Hess) and was prolonged significantly in grade 4 patients. Prolongation of CCT at the 5th day and 2 weeks after operation has been predictive in terms of the outcome at 2 months. Lengthening of CCT has appeared as a premonitor of clinical symptoms and shortening of CCT can be related to therapy such as induced hypertension. In operative examples, CCT indicates its values as a premonitor of ischaemic deficit, and some evidence has emerged that unduly deep hypotension may be reflected in prolongation of the CCT and in an increased likelihood of postoperative deficit.

In patients with posterior fossa tumour, we have found a significantly prolonged N14–P15 interval and also noted, for example, that in acoustic neuromas the changes clearly involve first the fillet above its decussation, since the N14–P15 prolongation is on the same side as the tumour after contralateral arm stimulation (unpublished results).

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ELECTRICAL MONITORING OF THE BRAIN IN INDUCED HYPOTENSION

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Slow activity in the e.e.g. increases in profound hypotension and then burst suppression appears. The duration of the isoelectric periods increases and if the arterial pressure is low enough the record becomes isoelectric. These changes have been shown to precede the release of potassium from the intra- to the extracellular space of the cerebral cortex in animal studies (Astrup et al., 1977). A period of isoelectric e.e.g. always preceded ischaemic cell damage in a neuropathological study by Brierley and colleagues (1980). It might therefore be expected that e.e.g. monitoring would be routine during the use of induced hypotension in clinical practice. This is not so because of the complexity of the apparatus and its sensitivity to electrical interference. Furthermore, in neurosurgery there is the problem of electrode placement.

The cerebral function monitor (CFM) is a simpler instrument which is more resistant to electrical interference in theatre. On the CFM all frequency information is lost and the e.e.g. is presented as a straight line, the height of which above base-line is proportional to the integrated electrical activity. This instrument has been used to monitor induced hypotension in clinical practice (Patel, 1981). There is still a problem with electrode placement in neurosurgery, and while it is possible to reposition the electrodes, information may then be lost from the critical arterial boundary zone.

Sensory evoked potentials have been used, but as Prior will discuss in this Symposium, these monitor only certain neuronal circuits which may not be the most sensitive to hypotension-induced ischaemia. Timing the evoked response from the upper cervical spine to the sensory cortex is a modification of the technique which avoids interference produced by alterations in peripheral nerve conduction time (Hume and Cant, 1978; Symon et al., 1979). Finally, the directly evoked cortical potential has been used with both stimulating and recording electrodes placed directly on the exposed cortex. Eisenberg and colleagues (1979) have monitored induced hypotension during neurosurgery with this technique, but it only gives information for the relatively small area of cortex on which electrodes are placed.

In a study in the cat Ishikawa and McDowall (1981) showed that depression of CFM occurred at greater arterial pressure during trimetaphan as compared with nitroprusside hypotension. This was shown to be a result of different degrees of cortical perfusion with the two drugs. Subsequent studies with a six-lead e.e.g. system have given further information which will be discussed.

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CRITICAL COMPARISON OF MONITORING E.E.G., CEREBRAL FUNCTION (CFM), COMPRESSED SPECTRAL ARRAY (CSA) AND EVOKED RESPONSE UNDER CONDITIONS OF DECREASED CEREBRAL PERFUSION

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The choice of technique with which to monitor the brain for signs of ischaemia during controlled hypotension in neuroanaesthesia depends upon several factors. Much of the anaesthetic literature overlooks the fact that different methods of handling e.e.g. data may be appropriate for different purposes. This is evident from a statistical comparison of various time and frequency domain techniques (Matoušek, Arvidsson and Friberg, 1978) for sensitivity to static or changing background activity abnormalities, altering level of consciousness and artefact. Methods must be practical and cost-effective, not disturbing or disturbed by neurosurgery, insensitive to artefact, indicating interference or malfunction and give unambiguous warning of critical decreases in perfusion with defined limits for threshold of ischaemic damage.

Whether there is risk of global or focal ischaemia, optimal recording sites and techniques can be derived from known topographical neuropathology of comparable human and experimental material. Thus cortical somatosensory evoked potentials can be appropriate during temporary carotid or middle cerebral artery occlusion which may damage the internal capsule, whilst processed e.e.g. from vulnerable cortical arterial boundary zone areas will best monitor controlled hypotension.

We have studied (a) 24 *Papio anubis* with moderate hypoxia and sequential bilateral common carotid artery occlusion (Brierley et al., 1980) with additional trimetaphan-induced hypotension in four; (b) 52 patients during cardiopulmonary by-pass and (c) 20 patients dying with or without brain damage after cardiopulmonary by-pass. Frequency analysis demonstrated subtle e.e.g. changes as a result of relatively decreased perfusion. Continuous analog computation of slow/fast r.m.s. power spectral density ratio (N. Etherington, unpublished data) gave a simple measure. Alternatively, a microprocessor-controlled CFM, the CFAM (Par Medex Ltd, Stevenage, Herts) (Maynard, 1979) as well as voltage information (weighted filter band-pass 2–27 Hz), provided frequency analysis by a multiple baseline crossing and integrating procedure and can also average and display evoked potentials. Time evolution of the display from these two methods has greater resolution than the CSA and related averaging methods which display sequential Fourier spectrograms of discrete epochs. Spectrograms inevitably mask brief events such as short electrical silences heralding onset of critical perfusion reduction. In our experimental and clinical studies, electrical silence persisted for 7–8 min during decreases in perfusion before ischaemic neuronal damage occurred. The total duration of silence together with recovery rate, however measured, correlated closely with clinical and neuropathological severity of brain damage. Frequency shift alone during ischaemia was never followed by brain damage. Thus, monitoring techniques to define critical limits can be restricted to voltage information, but the addition of measures of simple frequency gives helpful early warning.

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ASPECTS OF THE EFFECTS OF HYPOTENSIVE DRUGS ON INTRACRANIAL PRESSURE

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Most of the commonly applied techniques of induced hypotension have been shown to increase intracranial pressure (i.c.p.). The effects of nitroglycerine (TNG)-induced hypotension on i.c.p., vary considerably (Rogers et al., 1979; Burt, Verniquet and Homi, 1981). Therefore TNG was given to three groups of anaesthetized and artificially ventilated cats (group I = normoventilated; II = hyperventilated; III = normoventilated with a small supratentorial extradural balloon serving as an artificial space-occupying lesion, SOL) the i.c.p. measured via a needle in the posterior fossa during and after the administration of TNG was compared with a group of normoventilated cats (group IV) receiving sodium nitroprusside (SNP).

In figure 1, the change in i.c.p. (Δ ICP) is plotted against mean arterial pressure (% MAP). In the three groups of animals without intracranial pathology, i.c.p. increased moderately with no statistically significant difference between groups, whereas in the animals with SOL i.c.p. increased considerably. Maximum i.c.p. recorded in an individual experiment was 43.5 mm Hg.

As TNG was administered repeatedly to each animal with at least 30 min between each hypotensive period (which lasted for 5 min), eventually every animal with SOL showed dilatation of one or both pupils during the TNG-induced hypotensive phase. A more detailed analysis of the experiments with SOL revealed that i.c.p. in those experiments in which pupillary dilatation occurred remained high during the recovery phase or even increased further, indicating loss of autoregulation. Calculated cerebral perfusion pressure (CPP = MAP − ICP) in the experiments with pupillary dilatation was significantly less than CPP of the animals without signs of brainstem herniation.

The likely existence of a pressure gradient across the tentorium which has been demonstrated by Fitch and McDowall (1971) in similar experiments during the administration of halothane may have even further compromised cerebral supratentorial perfusion and caused cerebral vasoparalysis. Once vasoparalysis has occurred, i.c.p. may decrease with reduction of arterial pressure: this was observed in four experiments and may explain the conflicting results reported in the literature.

From our experimental results we conclude:

(1) In animals without intracranial pathology cerebral vasodilating agents such as sodium nitroprusside or nitroglycerine produce a small increase of i.c.p. (3–4 mm Hg).
(2) Prior hyperventilation does not modify this change.
(3) In experiments with artificial supratentorial space-occupying lesions i.c.p. increases markedly.
(4) In these animals i.c.p. remained increased during the recovery of the arterial pressure, indicating loss of autoregulation.

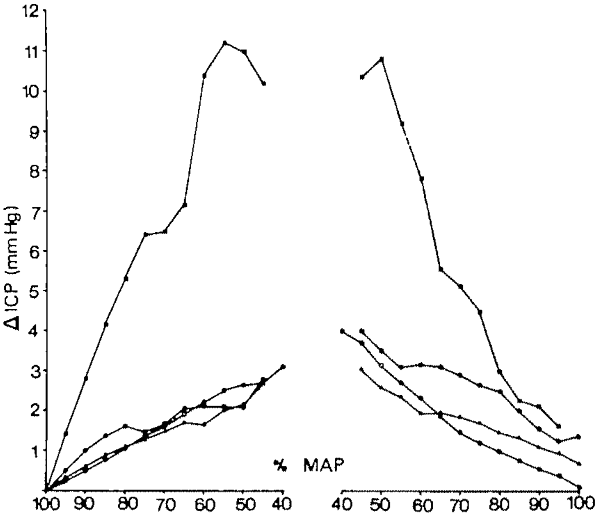

Fig. 1. Mean values of the change of intracranial pressure (Δ ICP) plotted against mean arterial pressure (% MAP). Group I (●) = TNG (normoventilation), $n = 23$; group II (▲) = TNG (hyperventilation), $n = 30$; group III (■) = TNG (normoventilation + SOL), $n = 47$; group IV (○) = SNP (normoventilation), $n = 12$.

(5) Brainstem herniation, indicated by pupillary dilatation may occur during the administration of TNG.

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SESSION IV

MORPHOLOGICAL ASPECTS

Chairmen: E. Betz and D. Graham

NEUROPATHOLOGY OF STAGNANT HYPOXIA CEREBRAL BLOOD FLOW AND THE CONCEPT OF THRESHOLDS OF ISCHAEMIA

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After an episode of cardiorespiratory arrest (stagnant ischaemic hypoxia) or severe hypotension (stagnant oligaemic hypoxia), the most important factor governing outcome is whether or not resuscitation can be achieved before irreversible hypoxic brain damage (HBD) has occurred. The extent and severity of the HBD can be identified and its distribution analysed by histological examination, provided the brain has been properly dissected after adequate fixation and the pathologist knows that certain parts of the brain are selectively vulnerable to hypoxia and is familiar with the microscopic appearances of the ischaemic cell process (Graham, 1977).

In ischaemic hypoxia resulting from generalized arrest of cerebral blood flow (c.b.f.) there is a characteristic pattern of selective vulnerability, *viz.*, diffuse neuronal necrosis in the neocortex, selective necrosis in the Sommer sector of the Ammon's horn, and variable involvement of the basal ganglia and thalami; in the hind brain there is characteristically diffuse necrosis of Purkinje cells but sparing of the brain stem nuclei. In oligaemic hypoxia as a result of a generalized reduction of c.b.f., hypoxic brain damage is concentrated in the neocortex along the boundary zones between the arterial territories of the cerebrum and cerebellum; there is variable involvement of the basal ganglia and the Ammon's horns are mostly spared. The majority of hypoxic episodes that result in histologically proven damage in the human brain cannot be adequately defined in physiological terms.

Whereas it has proved very difficult to study adequately monitored cardiac arrest in the laboratory, it has been possible to examine why hypotension may lead to accentuation of HBD in the arterial boundary zones. Many of these studies have been carried out by Brierley and colleagues (1980), who found that, under various physiological settings, an animal's tolerance to hypoxia is limited by the respiratory and circulatory systems and not by the energy resources of the brain itself.

The relationships between the blood supply of a nerve cell and its capacity to function and survive remains of fundamental importance. Thus the classical view states that, if cardiac arrest is of abrupt onset and occurs in a patient at normal body temperature, complete clinical recovery is unlikely if the period of arrest is more than 5–7 min. Clinical experience, however, suggests that some recovery can be expected; this has given rise to the hypothesis that certain cells probably survive in a state of structural integrity but functional paralysis. From this has developed the concept of ischaemic thresholds for complete electrical failure, potassium release and irreversible HBD (Astrup et al., 1977). More recent work, however, has shown that the actual thresholds in ischaemia may vary quite considerably, depending amongst other things upon species of animal, temperature, model and time-course of ischaemic insult.

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STRUCTURAL CHANGES IN THE BRAIN DURING CRITICALLY DECREASED BLOOD FLOW OR OXYGEN TENSION

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Experimental studies on cerebral ischaemia during the previous 10 yr have demonstrated considerable recovery of the energy state and of neurophysiological indices after prolonged periods of *complete* ischaemia. Accordingly, several morphological studies have failed to disclose extensive neuronal damage after *complete* ischaemia of 15–30 min duration (Jenkins et al., 1979). These results contrast with those showing more severe structural damage following similar periods of severe *incomplete* ischaemia or hypoxia (Brown and Brierley, 1972). Thus, paradoxically, the continued but inadequate supply of oxygen and substrate may be more detrimental than their complete cut-off, which implies that factors other than the degree of oxygen deficiency are important in the development of ischaemic nerve cell injury.

As reported in this Symposium by Dr Rehncrona excessive brain lactic acidosis has a deleterious effect on the post-ischaemic recovery of the energy state and neurophysiological indices. In the same model we analysed the light and electron microscopic changes (Kalimo et al., 1981) caused by severe incomplete cerebral ischaemia of 30 min duration (c.b.f. less than 5% of normal). In the experimental group with low lactate accumulation during the ischaemia (about 15 μmol g^{-1}) the alterations in the cerebral cortex at 0 or 5 min of recirculation were strikingly discrete: nearly normally dispersed nuclear chromatin, mild to moderate mitochondrial swelling and minor astrocytic oedema. These changes had virtually disappeared after 90 min of recirculation, and then only slight ribosomal disintegration was observed.

In contrast, the group with high lactic acidosis (tissue lactate about 35 μmol g^{-1}) already demonstrated structural changes by 0 or 5 min of recirculation: in all cells nuclear chromatin and cytoplasm were severely clumped, while mitochondria showed mild to moderate swelling. Interpretation of further tissue damage after 90 min of recirculation is handicapped by inadequate fixation because of the progressively impaired post-ischaemic cerebral circulation.

Remarkably, vascular obstruction was not observed during early recirculation, that is, primary "no-reflow" phenomena did not appear. Instead, in the high lactic acidosis group the cerebral circulation seemed to be impaired by secondary narrowing of capillary lumina, obviously related to increases in parenchymal and endothelial oedema resulting from the metabolic derangement that occurred during the ischaemia.

In comparison, structural changes were studied also during hypercapnic acidosis with arterial $P\text{CO}_2$ of 19.9–39.9 kPa, which decreases intracellular pH to about 6.65 unit. During such hypercapnia the energy state of the brain is altered minimally and only minor morphological alterations were encountered, suggesting that acidosis may be detrimental only if it occurs in conjunction with energy failure.

In conclusion, the brain might, under optimal conditions, tolerate markedly more severe anoxia-ischaemia than generally thought. Marked tissue lactic acidosis during cerebral ischaemia is one factor which impairs post-ischaemic recovery and it serves as one explanation for the paradox that severe incomplete cerebral ischaemia may sometimes be more deleterious than the complete ischaemia.

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THE SIGNIFICANCE OF LOW OXYGEN TENSIONS IN BRAIN TISSUE IN THE AETIOLOGY OF METABOLIC ALTERATIONS UNDER CONDITIONS OF CRITICAL BLOOD FLOW

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In order to study the thresholds for critical cerebral oxygen supply during arterial hypoxia and arterial hypocapnia, tissue PO_2 measurements and tissue metabolite assays were performed in the brain cortex of cats. In both experimental series the animals were lightly anaesthetized with sodium pentobarbitone 25 mg kg^{-1} i.v., completely immobilized and artificially ventilated. After a bilateral craniotomy, rCBF and tissue PO_2 were measured in the brain cortex using the krypton-85 clearance technique and multiwire surface PO_2-microelectrodes, respectively. In frozen tissue samples taken from the cortical areas under investigation the concentrations of different metabolites were determined. Results are presented in table I.

In the first group of experiments the arterial PO_2 was decreased stepwise from normal values to about 6.7 kPa and 4.0 kPa at normal arterial carbon dioxide tension. Both hypoxic values were maintained for about 30–45 min. Under moderate arterial hypoxia, simultaneously with an increase of rCBF, there was a shift of the tissue PO_2 frequency distribution to low values. A significant increase of tissue PO_2 values between 0 and 0.33 kPa was found when the arterial oxygen tension reached values less than approximately 6.7 kPa. This indicates the presence of tissue hypoxia with anoxia in single cells. The results of the metabolite assays confirm the above conclusions. The tissue concentrations of lactate and pyruvate and the lactate/pyruvate ratio were increased, while the concentration of phosphocreatine was decreased significantly.

Under conditions of pronounced arterial hypoxia the alterations in cortical blood flow, tissue PO_2 and the concentrations of tissue metabolites were augmented. In addition, the ATP concentration was decreased significantly and the concentrations of ADP and AMP increased. The results demonstrate that, in spite of the increase in rCBF, a severe imbalance between oxygen supply and demand was present in the cortex.

In the second experimental group the cats were hyperventilated to decrease the arterial carbon dioxide tension to about 2.7 kPa and 1.6 kPa. Moderate arterial hypocapnia induced the typical reaction of rCBF. Because of the blood flow decrease and the displacement of the blood oxygen dissociation curve to the left, the tissue PO_2 histograms were shifted to lower values. However, no deficiency of oxygen could be established. The frequency of tissue oxygen tensions in the range 0–0.33 kPa did not increase. Decreasing the arterial carbon dioxide tension to less than 2.0 kPa induced pronounced tissue hypoxia in the cortex. The number of tissue oxygen tensions of 0 and near 0 kPa increased significantly. At the same time the tissue concentration of phosphocreatine was found to be significantly less than the normal value, while the concentrations of lactate and pyruvate and the lactate/pyruvate ratio were above baseline.

TABLE I. *Effect of moderate (Pa_{O_2} 6.7 kPa) and severe arterial hypoxia (Pa_{O_2} 4.0 kPa) and of severe arterial hypocapnia (Pa_{CO_2} 1.6 kPa) on tissue metabolites in the brain cortex of cats. Metabolite concentrations are given as µmol g^{-1} wet weight. (Mean values ± SEM). PCr = phosphocreatine*

	Normoxia-normocapnia	Moderate hypoxia	Severe hypoxia	Severe hypocapnia
Lactate	1.244±0.141	10.166±2.727	23.737±3.674	5.915±1.094
Pyruvate	0.096±0.020	0.247±0.044	0.264±0.019	0.220±0.027
PCr	4.590±0.20	2.240±0.52	1.070±0.25	3.380±0.25
ATP	2.530±0.15	2.260±0.08	1.960±0.22	2.580±0.15
ADP	0.330±0.30	0.530±0.06	0.750±0.11	0.540±0.08
AMP	0.040±0.01	0.180±0.03	0.150±0.03	0.070±0.02

SESSION V

CLINICAL ASPECTS

Chairmen: E. Gordon and U. Braun

CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION DURING CONTROLLED HYPOTENSION IN NEUROSURGICAL PATIENTS

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Several studies in animals have shown that sodium nitroprusside can increase cerebral blood flow and intracranial pressure and abolish cerebral autoregulation of blood flow during controlled hypotension. However, there are conflicting data concerning the effects of nitroprusside on cerebral blood flow in man. This study was designed to investigate the effects of nitroprusside-induced hypotension on cerebral blood flow and oxygen consumption in 10 patients undergoing surgery of cerebral aneurysms. All patients were premedicated with diazepam. Anaesthesia was induced with methohexitone and maintained with nitrous oxide in oxygen and fentanyl. Muscle relaxation was achieved with pancuronium. The lungs were ventilated mechanically; Pa_{CO_2} was maintained at 4.8–5.3 kPa. Mean arterial pressure was reduced to 50 mm Hg by i.v. infusion of nitroprusside after opening of the cranium. Measurements were recorded and blood samples were taken 15 min before induction of hypotension (I), during nitroprusside administration 5 min after stable hypotension had been achieved (II), and 15 min after termination of nitroprusside infusion (III). Measurements included: cerebral blood flow (c.b.f.), using the argon-washin technique, cardiac output (thermodilution), mean arterial pressure and heart rate. Cerebral venous and arterial blood samples were analysed for haemoglobin concentration, blood-gas tensions and electrolyte concentrations. Cerebral oxygen uptake ($CMRO_2$) was calculated by multiplication of arterial–cerebral venous blood oxygen content difference by cerebral blood flow. Cerebral blood flow averaged $56\pm6\,\mathrm{ml\,min^{-1}}$ per 100 g before inducing hypotension (I). I.v. infusion of nitroprusside produced hypotension but did not significantly alter c.b.f. (II: $61\pm7\,\mathrm{ml\,min^{-1}}$ per 100 g). C.b.f. remained virtually at preinfusion values upon cessation of infusion (III: $53\pm6\,\mathrm{ml\,min^{-1}}$ per 100 g). Cerebral oxygen uptake averaged $3\pm0.2\,\mathrm{ml\,min^{-1}}$ per 100 g before hypotension and did not change significantly during controlled hypotension (II: $3.3\pm0.3\,\mathrm{ml\,min^{-1}}$ per 100 g). After termination of hypotension $\mathrm{CMRo_2}$ slightly decreased (III: $2.7\pm0.3\,\mathrm{ml\,min^{-1}}$ per 100 mg) probably because of the effects of anaesthesia. In two patients nitroprusside produced a 20% increase in cerebral blood flow with no change in cerebral oxygen consumption together with a marked increase in cardiac output and heart rate.

These results suggest that global cerebral blood flow and cerebral oxygen consumption are maintained during nitroprusside-induced hypotension in neurosurgical patients. Our data also indicate that nitroprusside may increase cerebral blood flow. Therefore, nitroprusside should not be used for reducing arterial pressure in patients with low intracranial compliance.

ORGAN-SPECIFIC LIMITATIONS OF INDUCED HYPOTENSION

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Interest in possible organ damage produced by induced hypotension is directed to the brain and the heart. The cerebrum is treated comprehensively in this Symposium. The heart remains to be discussed.

In 1978 a 49-yr-old male patient underwent clipping of a cerebral aneurysm. He had no history of cardiac disease and clinical examination revealed no abnormalities. Hypotension was induced with halothane. Mean arterial pressure was 80 mm Hg (invasive measurement). Suddenly, before an attempt at clipping could be made, there was a decrease in arterial pressure to a mean value of 50 mm Hg followed by cardiac arrest. Attempts at resuscitation were unsuccessful. Pathology revealed coronary artery disease (CAD): arteriosclerotic disease of all branches of the coronary system, almost complete stenosis of the Ramus interventricularis and 80% stenosis of the Ramus circumflexus of the left coronary artery.

It is remarkable to note that the patient gave no history of CAD, but this feature is not unusual. In 1978 there were 723 219 deaths in Germany. Of these there were 141 528 cases of ischaemic heart disease (20%). According to an American review (Lown, 1979), there was a high frequency of sudden cardiac death (SCD) among all fatalities associated with ischaemic heart disease: 40% of SCD in ischaemic heart disease in Germany 1978 represents almost 57 000 patients (USA 438 000). Of these, 25% (Germany 14 000, USA 109 500) gave no history of CAD. There is no doubt that controlled hypotension is a threat to life in a patient with CAD.

Even with very careful history-taking and thorough preoperative evaluation, there remains lack of confidence that it is possible to exclude all CAD-patients from hypotension.

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FOR AND AGAINST HYPOTENSION IN NEUROSURGERY

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The introduction of the technique of controlled deliberate hypotension in the late 'forties started a wave of enthusiasm among surgeons who saw the possibility of performing extensive operations, even on highly vascular tumours, in a practically bloodless operative field with no major blood loss. However, it soon became evident that this technique can initiate severe and, sometimes, fatal complications. Therefore, its use has been gradually restricted to those procedures in which the operation could not be performed otherwise without greatly endangering the life of the patient; in such circumstances, the advantages of hypotension outweigh its risks. Documentation of these risks has been extensive, particularly in the early period of this technique: coronary thrombosis, thrombosis of the retinal artery with subsequent amaurosis, renal failure and signs of liver damage. It is now evident that these severe complications were the result of a combination of the lack of experience of anaesthetists and the inadequacy of the drugs available. Today none of these shortcomings is valid, except that patients with advanced clinical signs of arteriosclerosis, previous history of thrombosis in vital organs, severe anaemia and a low blood volume should not be exposed to the additional risk of hypotension.

In neurosurgery, controlled hypotension went through the same phases of use as in other surgical specialties. At the beginning neurosurgeons not only hoped to be able to control bleeding during dissection of vascular tumours, arteriovenous malformations and arterial aneurysms, but also to avoid or diminish brain oedema. This situation has changed substantially during recent years, and in most clinics the use of controlled hypotension is restricted to patients with arterial or arteriovenous malformations.

When a need for induced hypotension has been agreed between surgeon and anaesthetist, the risk of complications has to be evaluated in the light of the severity of the condition for which the patient is to undergo surgery. Existing pathological conditions should be corrected before surgery. Extremes of age, coronary and cerebrovascular disease, thrombophlebitis, hypertension, cardiac arrhythmias, pulmonary, renal and hepatic disease add to the hazards of hypotension, and the decision can sometimes be difficult. A ruptured aneurysm is, however, a life-threatening disease, and therefore the high risk is justifiable.

Another crucial point relevant to the problem is the level and the duration of hypotension. Opinions on these points are highly divergent, depending probably on the fact that our present knowledge of the tolerance of cerebral tissue towards various degrees of hypoxia and ischaemia is still rudimentary. It is to be hoped that new results in this field will give us better tools in defining the margins of safety, and thus will enable us to diminish further the risks and complications still inherent in this technique.

As a last point, the absolute necessity of a well-trained team of surgeon and anaesthetist, and a highly competent postoperative and intensive care unit has to be emphasized as a prerequisite to a successful operation under controlled hypotension.

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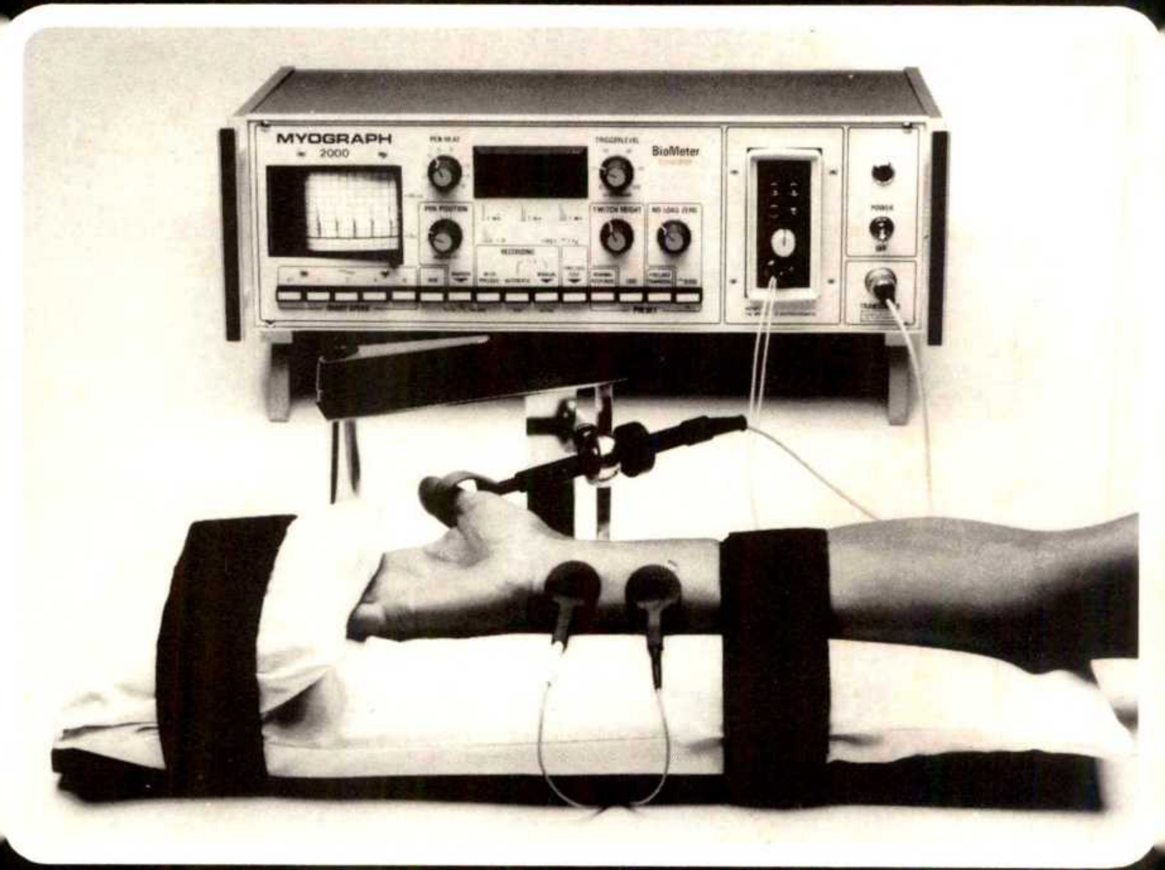

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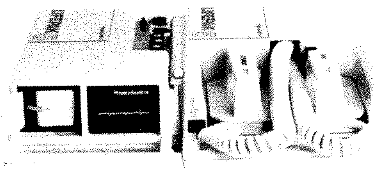

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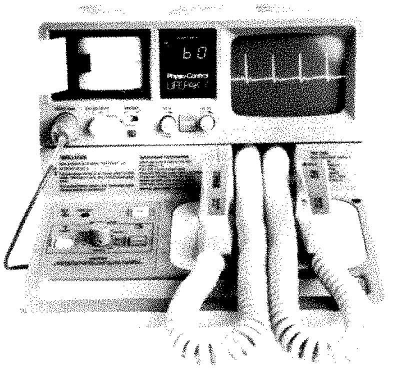

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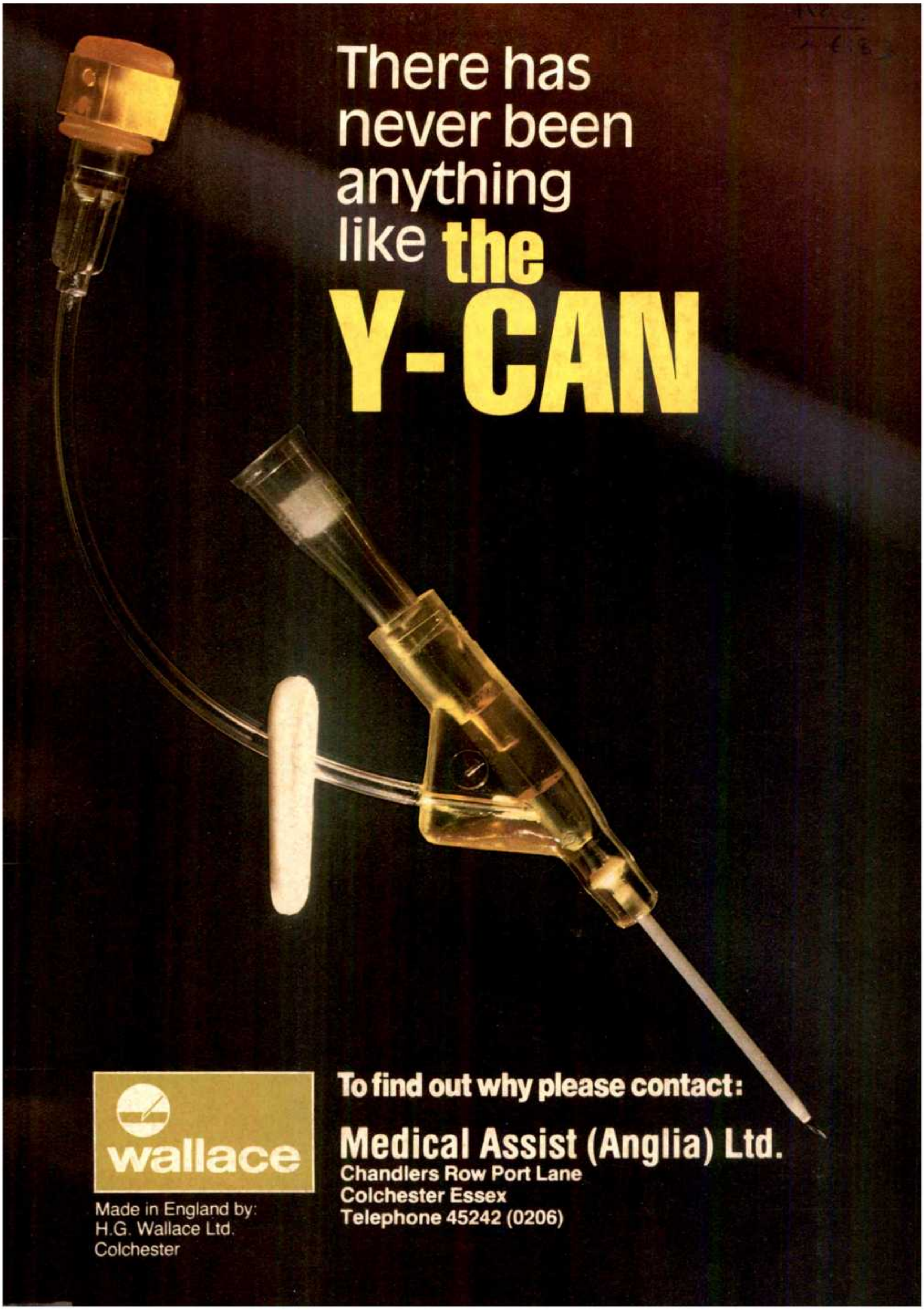

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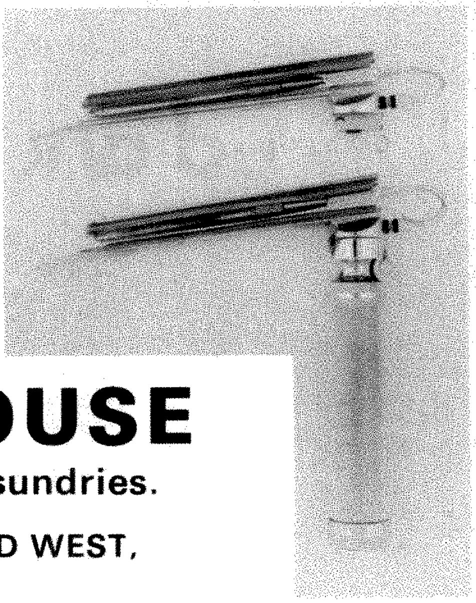

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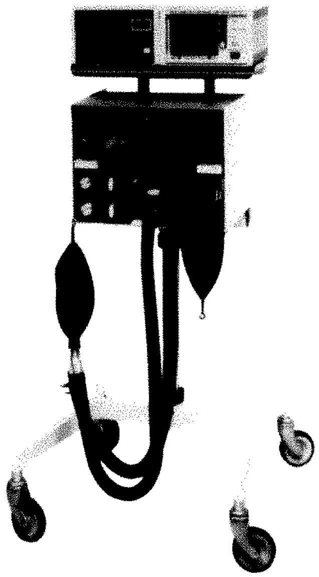

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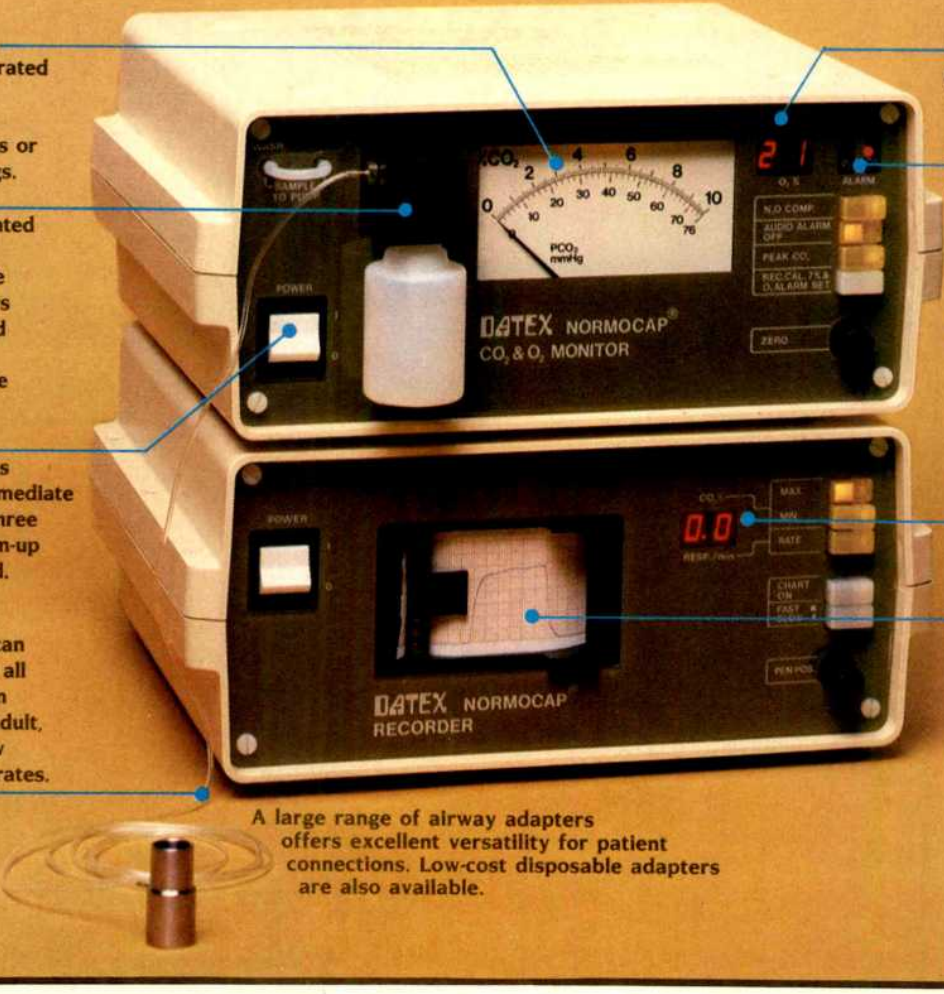

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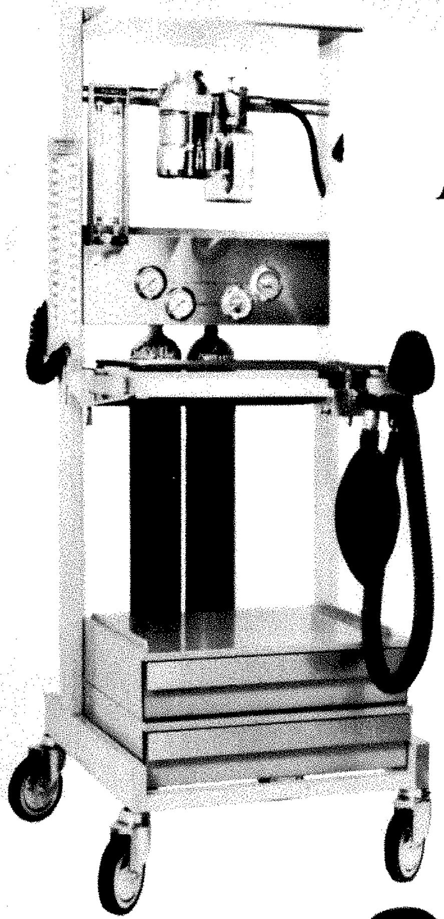

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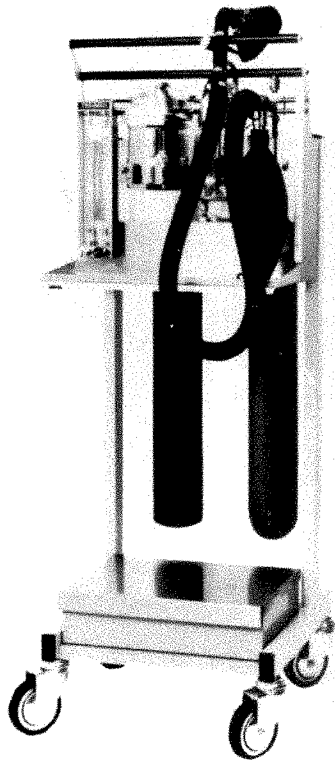

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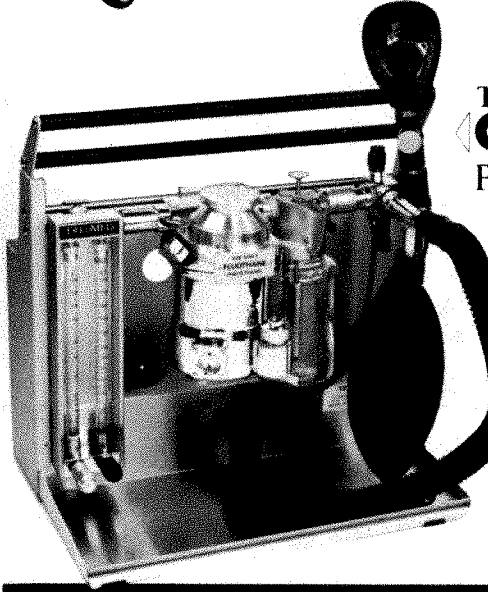

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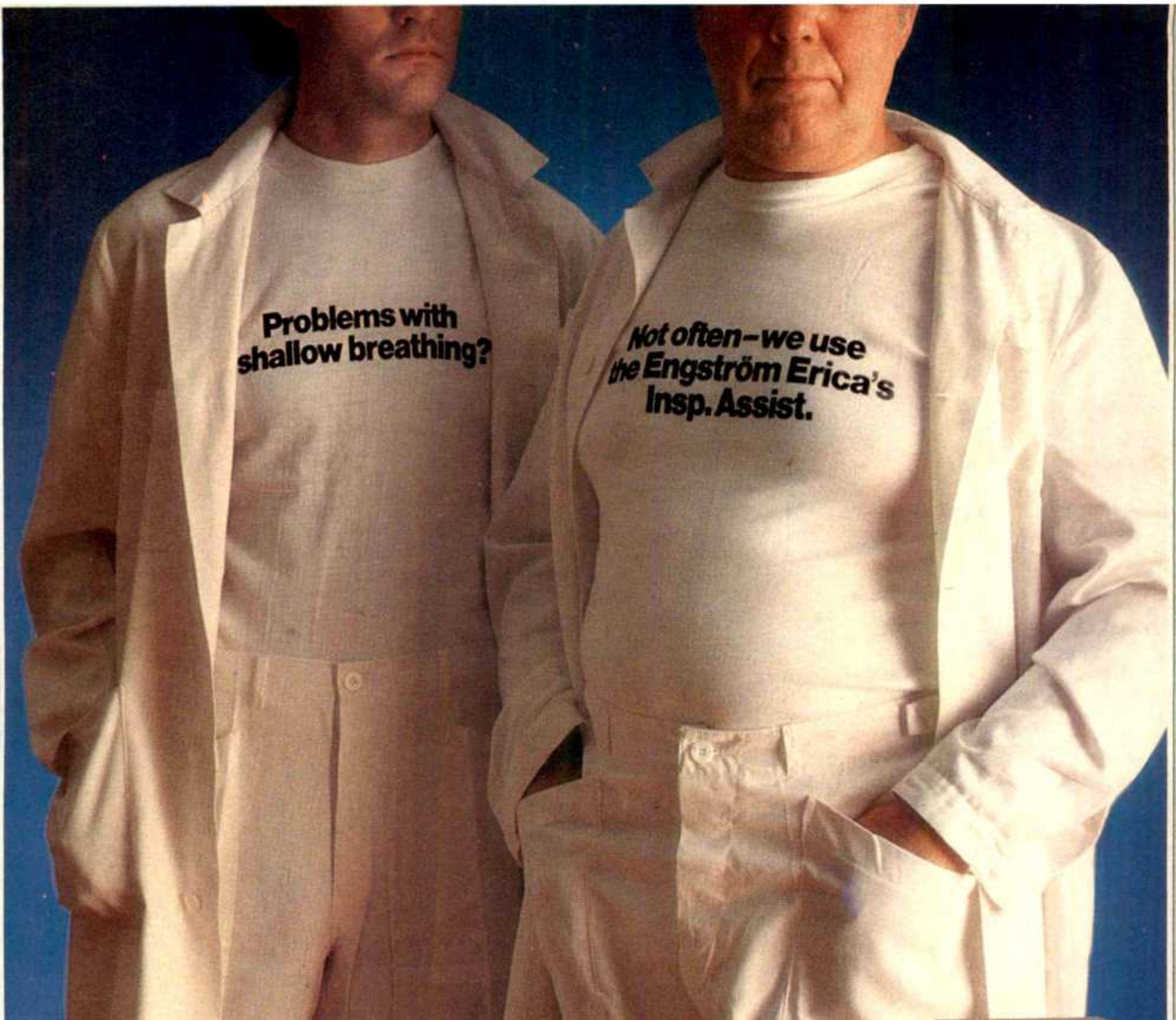
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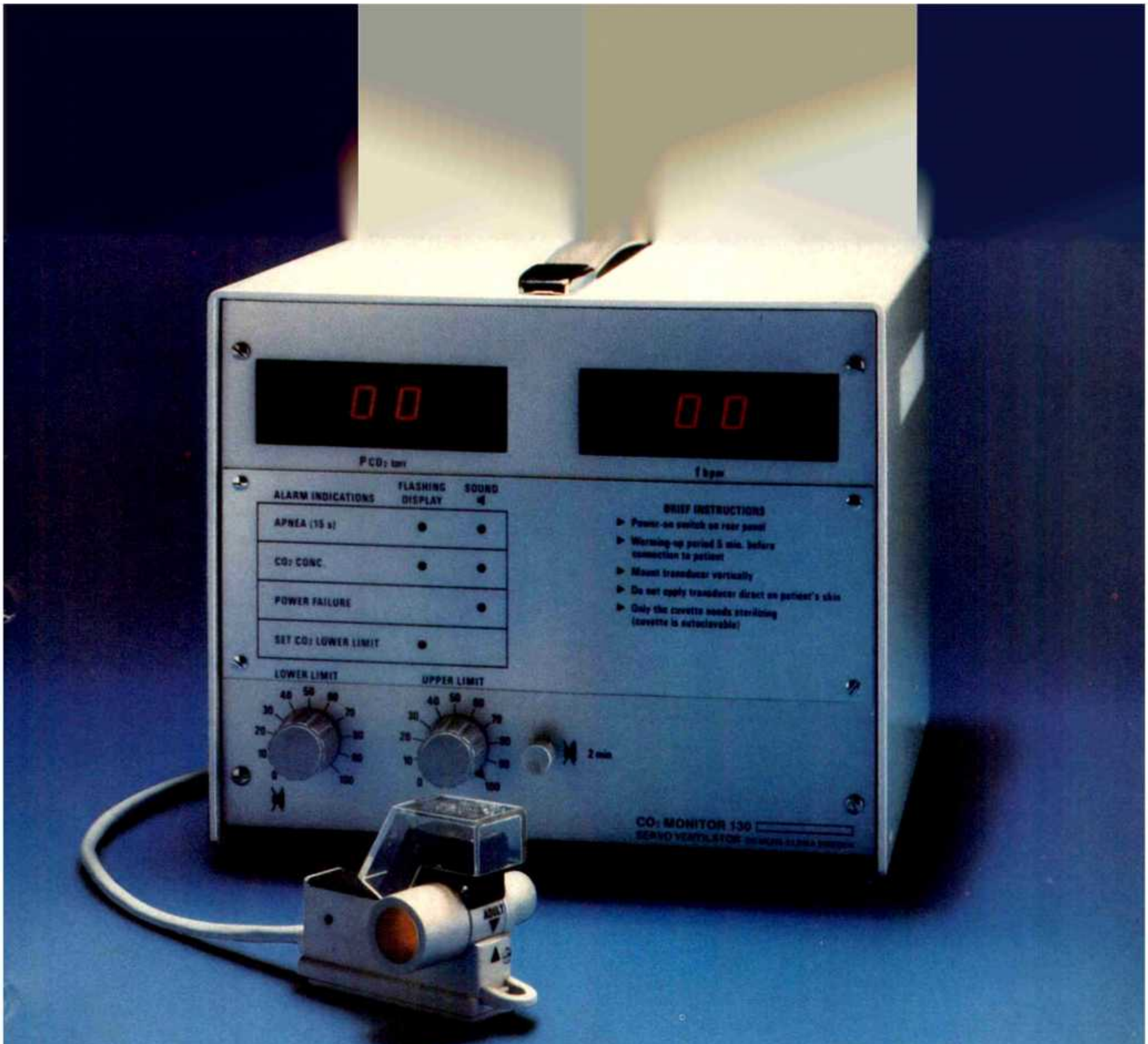
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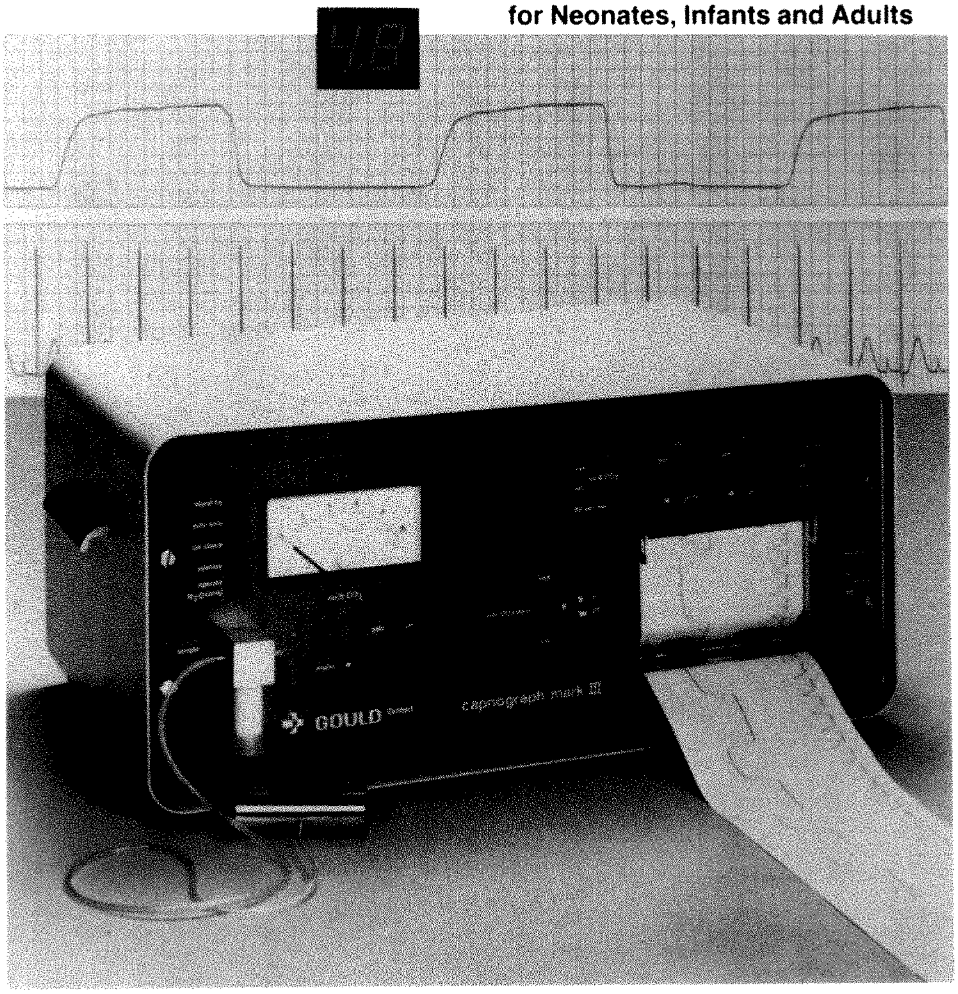

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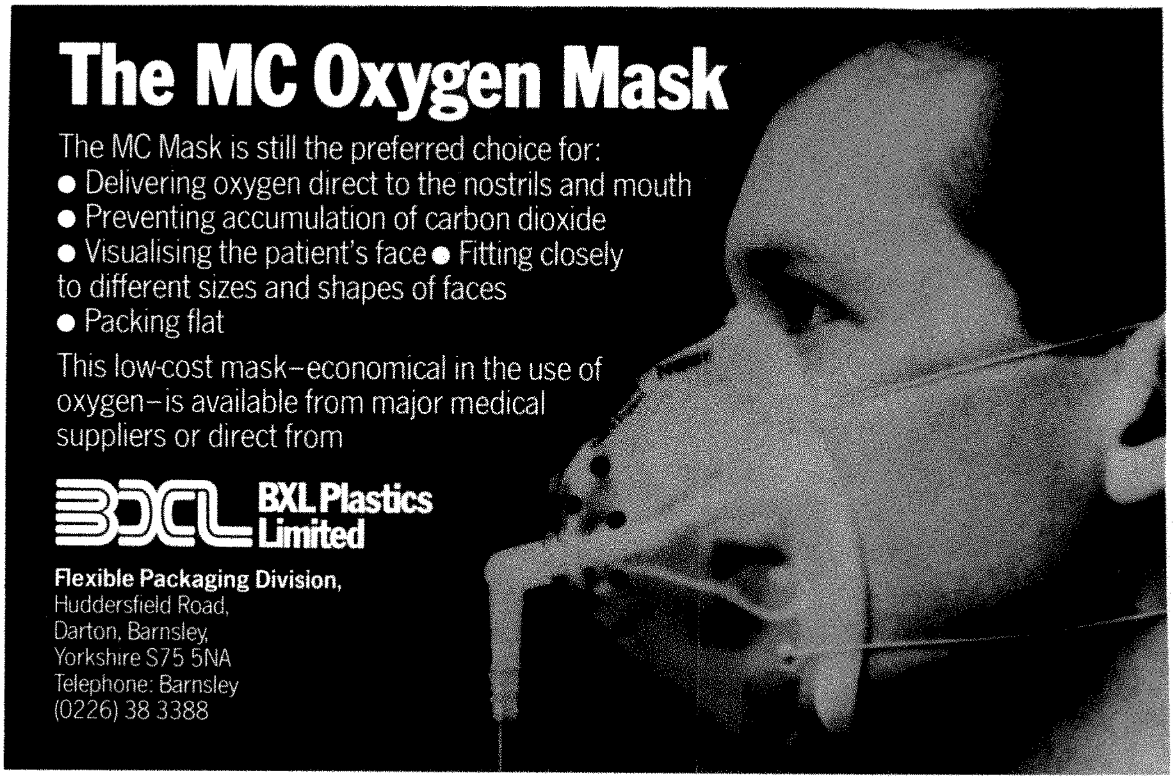

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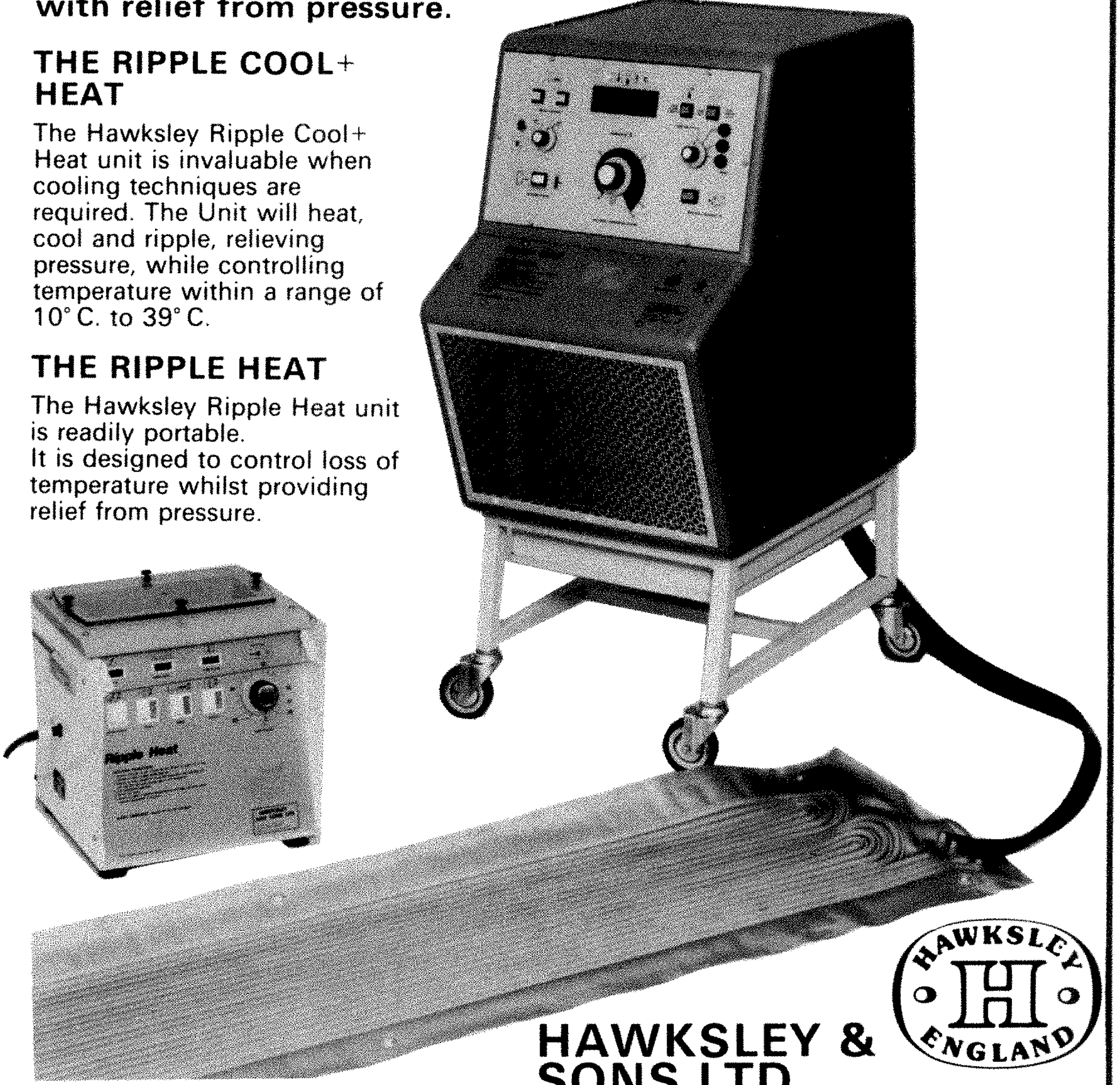

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EDITORIAL

THE F.F.A.R.C.S. EXAMINATIONS

The Faculty of Anaesthetists of the Royal College of Surgeons of England proposes sweeping changes in the format of the F.F.A.R.C.S. examinations with a target date in 1984. It is likely that some of the diploma examinations in other countries will change similarly.

In a statement published in the January 1982 issue of *Annals of the Royal College of Surgeons of England* (page 69) the Board of Faculty gives an outline of the proposals:

(1) The first part [of the examination] will include basic anaesthetic practice, medicine and surgery in relation to anaesthesia, and basic sciences relevant to these subjects. This examination may be taken after 1 year in approved anaesthetic posts.

(2) The final examination will contain applied basic sciences and clinical measurement together with principles of all aspects of anaesthetic practice including intensive therapy and pain relief. A clinical examination will remain in the final. A multiple-choice question paper in the basic sciences must be passed before candidates are admitted to the rest of the final examination, the entry requirements for which remain unchanged.

(3) The target date for these changes in 1984 and guidance for teachers and candidates will be published at least 2 years in advance of any change.

It is no secret that there has been strong opposition to the Board's proposals, notably from the ranks of academic anaesthetists and of examiners. Equally, however, there was strong support for change, particularly among consultants responsible for training in the district general hospitals. They apparently felt uneasy as tutors in the basic sciences for those presenting for the existing first part of the F.F.A.R.C.S. examinations. These consultants are attracted by a primary examination which is closely linked to the clinical training undertaken in the first year in the specialty. One can imagine also that the proposals will be popular with the trainees themselves.

One aspect of the change which will be universally popular is the disappearance of the clinical measurement portion of the present primary examination. This ill-defined component seems to have been seriously out of control for some years, with a range of questions that occasionally inflicted punishing pressures on the candidates while not noticeably improving the overall understanding of measurement in the specialty.

While the specialty may look confidently for useful returns from the new proposals, there are important potential pitfalls of which the Board of Faculty in particular and the specialty in general should remain aware. The worth of the present F.F.A.R.C.S. qualification is attributable in considerable measure to the high standard of examination in the basic sciences of physiology and pharmacology. It is the profession of these in the academic setting of the examination that separates the learned specialist from the technician or artisan. On the other hand, the level of excellence that may be expected of candidates is determined more by the efforts of the candidates themselves than by the mere listing of the subject on a timetable. If every candidate is capable of performing to only a mediocre level, the threshold of acceptability must lie within that level otherwise the examination would become a nonsense in which no one passed. A justified fear with the new proposals is that the attenuation of the basic sciences through the whole exam timetable, instead of the intense period of study required for the present primary, will lead to a dilution of capability in physiology and pharmacology in anaesthetists of the future. The best safeguard against this would be a preparedness of those who train to continue to base early training on adequate teaching of the basic sciences. Given the right emphasis, the anxiety expressed above may be groundless and the new proposals could yield a nett strengthening of basic science capability.

The alteration of the content of the primary examination to reflect the examinee's clinical experience more closely must not lead to a misconception as to the purpose and limitations of the examination. The examination is an academic hurdle in which the candidate professes knowledge and understanding of his subject acquired through practical experience, reading, lectures and seminars. Success signals achievement of a suitable standard, but this should never be confused with ability to perform the clinical craft of anaesthesia. The examination setting, as we know it, is not the place for satisfying criteria of that kind. That responsibility rests locally—and totally—in the hospital charged with training and reviewed regularly by the Faculty as a suitable institution for that purpose.

Alastair A. Spence

Br. J. Anaesth. (1982), 54, 267

ANAESTHETIC EMERGENCY SERVICE AT THREE HOSPITALS—A DECADE OF CHANGE

E. MAJOR, T. BATES, A. M. C. JENNINGS, D. A. NIGHTINGALE, T. H. TAYLOR, P. D. BOOKER AND K. R. L. EVANS

SUMMARY

The results of a 6-week survey of anaesthetic emergency work completed in 1978 are compared with those from an earlier survey in 1967. Three hospitals were sampled, an undergraduate teaching hospital, a district general hospital and a specialized paediatric hospital. At all three hospitals emergency workload increased relative to the population served, with intensive therapy accounting for much of the extra demand. The consequences for the provision of an anaesthetic service are discussed.

In a series of papers, Taylor and others (1969a–e) reported on the emergency workload of three anaesthetic departments during an 8-week period surveyed in the autumn of 1967. The hospitals involved were an undergraduate teaching hospital (The London), a general hospital (Northampton) and a specialist paediatric hospital (Alder Hey Children's Hospital, Liverpool). The authors subjected the data to statistical analysis and used Queuing Theory to suggest ways of deploying staff to best advantage in these three very different departments.

Since that time many changes have taken place including reorganization of the health service, shifts of population, changes in the birth rate and financial constraints. The emergency anaesthetist may nowadays be asked to give essentially new services, for example anaesthesia for transplant surgery or obstetric analgesia. Because of these changes it seemed prudent to reassess the emergency anaesthetic commitment at the three hospitals.

The survey reported here involved the same three anaesthetic departments. The survey period was 43 days at The London, 49 days in Northampton and 42 days in Liverpool beginning on the same day (November 21, 1978) and continuing through the Christmas and New Year holiday period.

METHOD OF DATA COLLECTION

In all three hospitals data were collected on all emergency anaesthetic calls. On-call staff were also called on occasionally to anaesthetize non-emergency cases out of hours. When this occurred the calls were recorded because occupancy of on-call staff, whether with emergencies or not, does affect the standard of service. During the ordinary working day, however, a number of emergency cases may be put on to the routine planned lists, perhaps as identifiable extras, perhaps not. Wherever such additions were identified they were included. Without a much more elaborate survey involving data collection for all cases—including planned—it was not possible to obtain strict comparability either between hospitals or between surveys, but the errors so introduced are considered to be small.

One of the authors daily checked the data collected at each hospital and entered them on to a computer file. Cross-checking of theatre records ensured that no cases labelled as emergencies were missed.

The following details of each emergency request were recorded:

(1) The hospital and date
(2) The time of initial request for service
(3) The urgency stated
(4) The urgency as assessed by the responding anaesthetist

E. MAJOR, M.B., B.S., F.F.A.R.C.S., T. H. TAYLOR, M.B., B.S., F.F.A.R.C.S. (Anaesthetics Unit), T. BATES, M.SC. (Operational Research Department), The London Hospital, Whitechapel, London. A. M. C. JENNINGS, M.B., B.CHIR., F.F.A.R.C.S., D.A., K. R. L. EVANS, M.B., CH.B., F.F.A.R.C.S., Department of Anaesthesia, Northampton General Hospital, Northampton. D. A. NIGHTINGALE, M.B., B.CHIR., F.F.A.R.C.S., D.A., P. D. BOOKER, M.B., B.S., F.F.A.R.C.S., Department of Anaesthesia, Alder Hey Children's Hospital, Liverpool.

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(5) The time arranged for starting the case
(6) The time of starting the case
(7) The time of finishing the case
(8) The type of work
(9) The grade of the responding anaesthetist
(10) The grade thought appropriate for the case
(11) The location and activity of the responding anaesthetist when called

This was a system of recording as similar as possible to that used in the 1967 survey. In addition the urgency of each request was assessed according to the following scheme which was also as used in 1967.

Emergency categories

(1) *Immediate*—requiring service within 3 min, for example cardiac arrest
(2) *Urgent*—requiring service within 15 min, for example fetal distress
(3) *Emergency*—requiring service within perhaps 90 min, for example perforated appendix
(4) *Low priority emergency*—capable of waiting several hours, for example uncomplicated fracture
(5) *Cold surgery*—performed out of hours by someone on-call

At each hospital one of the authors of the original 1969 paper tried to ensure consistency of recording between the two surveys.

The hospitals

Administrative changes occurring between the two surveys resulted in changed patient populations and staffing levels, necessitating a description of both at each hospital.

The anaesthetic department at The London Hospital in 1967 provided emergency cover for the main hospital of 741 beds and a 38-bed maternity home 7 miles away. Emergency staff based at the main hospital consisted of a resident house officer, a resident senior house officer (SHO) and a registrar (who slept in the ITU) together with a senior registrar and two consultants on-call from home, one for theatre anaesthesia and the other for intensive therapy.

By 1978 the maternity home had passed to another health district and The London had become integrated with the nearby Mile End Hospital, which consisted of 380 beds including 176 surgical and 54 obstetric, and which had its own casualty department. In order to cope with this extra workload a second registrar was on-call from home. Apart from this the deployment of staff was identical to that in 1967.

At Northampton General there had been no change in on-call staffing between surveys with a consultant on-call from home and an SHO and registrar either resident in or very close to the hospital. Both in 1967 and 1978 the anaesthetic department at Northampton General provided routine service for two smaller hospitals in the town, but all emergencies were treated at the main hospital. The number of acute beds available at Northampton General had decreased slightly between surveys (table I).

Deployment of on-call staff at Alder Hey was unaltered from 1967 to 1978, with a single resident anaesthetist of SHO, registrar or senior registrar status supported by a senior registrar and consultant on-call from home. The number of available beds had reduced by 1978, but the annual rate of admissions and discharges had increased (table I). This was accounted for by the establishment of a day surgery service with a throughput of about 2400 patients annually.

In 1967 at Northampton and Alder Hey intensive therapy unit (ITU) calls were initiated by nursing staff in the units. At any time of day they called on anaesthetic staff known to be on duty not only for ITU but also for the rest of the service. Each call was thus a defined event, the timing of which could be recorded. At Northampton in 1978 these arrangements and the number of ITU beds (five) were unchanged. At Alder Hey the ITU had increased from six to eight cots between the surveys and the ITU staffing arrangements had also changed. In 1978 the ITU had a registrar exclusively reserved during ordinary working hours Monday–Friday, although he was liable to be called out of ITU for cardiorespiratory arrests elsewhere. Work done in ITU by this daytime registrar was not included. At 17.00 h the ITU and resuscitation duties were taken over by the on-call registrar who thereafter recorded all requests for his services.

At The London (during both surveys) work in the six-bedded ITU between the hours of 08.30 and 17.00 was not recorded since a registrar was specifically reserved for this service. In 1967 "out of hours" requests for ITU service were documented individually, but in 1978–79 this proved impossible because of increased pressure of work and a different system of recording was used. In order that the registrar had time to perform his clinical duties and not be overburdened by form-filling and time-keeping, he merely indicated on a log sheet whether "working" or "not working" during each quarter-hour of his on-call period. The results thus take no account of whether he was controlling a dangerous arrhythmia or merely taking routine blood samples. It was felt that to itemize each duty, time it, and record it would probably result in poor co-operation and thus inaccurate data. All cardiac arrest calls and emergency theatre patients at The London were recorded individually.

RESULTS

The overall picture

During the period of the survey The London, Northampton and Alder Hey recorded 459, 427 and 174 requests respectively, for service other than intensive therapy. In addition Northampton and Alder Hey recorded 65 and 51 requests for service in the ITU.

The emergency workload at Mile End Hospital, which by 1978 was served by the anaesthetic department at The London, amounted to 111 cases in 6 weeks. None of these requests was Priority 1 and only eight were Priority 2. Emergency service at Mile End Hospital occupied only 13% of the total service time and 96% of this time was occupied with low priority emergencies. The Mile End Hospital workload is included in The London Hospital data throughout this paper.

Table I demonstrates that the amount of emergency work as measured by service time had increased both at The London and at Northampton, but at Alder Hey there was a slight decrease during the period studied.

Not only had the amount of work changed over the decade, but the pattern of work had changed too (table II). In 1967 emergency ITU work occupied only 7–8% of the service time at The London, but this increased to 40% in 1978. At Northampton and Alder Hey the commitment to intensive therapy had also increased markedly.

In 1967 general/abdominal surgery was the greatest user of anaesthetic time at all three hospitals. In 1978, however, both ITU and trauma/orthopaedics had overtaken general/abdominal work at The London, although at Northampton and Alder Hey general surgery remained the largest single commitment.

The number of calls and amount of time spent attending cardiorespiratory arrests had decreased sharply over the years at both The London and Alder Hey. At Northampton, on the other hand, both the number of arrest calls and the total time spent on this activity had increased.

TABLE I. *Summary of data obtained at three hospitals in two surveys separated by 11 years. *Includes 2435 day patients*

	London		Northampton		Alder Hey	
	1978–79	1967	1978–79	1967	1978–79	1967
Total acute beds	1031	703	538	562	461	650
Surgical	487	325	289	300	232	381
Obstetric	92	76	96	73	—	—
Births ($\times 10^3$)	2.5	2	4.3	3.0	—	—
Admissions/discharges ($\times 10^3$)	30.9	18	21.9	16.4	15.9*	14.2
On-call staff						
Resident	3	3	0	0	1	1
Non-resident	2	1	2	2	1	1
Consultant	2	2	1	1	1	1
Days sampled	43	56	49	56	42	56
Episodes/day	14	7.8	10.04	8.09	5.36	6.9
Mean duration (min)	87	63	48	33	50	49
Mean daily service time (h)	20.3	8.2	8.03	4.45	4.46	5.63
Mean daily service time as percentage of 1967 figure	247.6	100	180.45	100	79.2	100

TABLE II. *Average daily service times for the main specialties in 1978 and the ratio of these to 1967 equivalents (not all are listed) (1978 : 1967)*

1978	The London		Northampton		Alder Hay	
	Hours /day	Ratio 1978/1967	Hours /day	Ratio 1978/1967	Hours /day	Ratio 1978/1967
Cardiorespiratory	0.4	0.6	0.26	1.3	0.1	0.2
ITU	8.4	13.0	1.0	2.8	1.2	3.7
Midwifery	0.7	0.7	1.0	2.0	—	—
General/abdominal surgery	3.2	1.4	2.7	1.5	1.4	0.7
Thoracic	0.3	1.0	—	—	0.05	0.1
Neurosurgery	1.1	1.3	—	—	0.6	0.6
Trauma/orthopaedic	3.2	6.0	1.5	1.9	0.45	0.9
Dental	0.4	1.8	—	—	0.1	0.5
Neonatal	0.02	0.4	—	—	0.4	0.3
Consultation/advice	0.4	1.4	0.1	1.9	—	—
Obstetric extradurals	0.5	—	0.6	—	—	—
Renal transplantation	0.2	—	—	—	—	—

Since 1967 a few types of call have been added to the emergency workload, essentially because a new treatment had developed. These included anaesthesia for renal transplants, and extradural analgesia for obstetrics. Since 1967 an extradural service had been established in Northampton and 51 cases—almost exactly one a day—were presented as emergencies. At The London 34 requests were received by the on-call anaesthetist for extradural analgesia in labour.

Distribution of work between days within the survey

Whereas in 1967 the period of survey was chosen so as to avoid public holidays, in 1978–79 it was chosen so as to cover both Christmas and New Year.

Using Chi-square testing, the number of cases per day were examined to see if there was any difference apparently resulting from the day of the week and to see what difference the major public holidays made.

At The London and Alder Hey the day of the week during a non-holiday week made no statistically significant difference ($P = 0.33$ and 0.27 respectively). At Northampton a tendency for greater daily totals towards the end of the week is suggested by the 1978 data ($P = 0.05$).

For the period of the whole survey the workload again did not alter significantly with the day of the week at The London ($P = 0.89$) or Alder Hey ($P = 0.21$) but at Northampton there was a significant daily variation in workload ($P = 0.17 \times 10^{-3}$) largely accounted for by increases in general surgery, midwifery and trauma/orthopaedics on Fridays and Saturdays throughout the survey.

During the holiday period of December 22, 1978 to January 2, 1979 the workload at Alder Hey was again independent of the day of the week ($P = 0.45$) and the total workload over Christmas and New Year was not markedly different from the non-holiday period. At The London the workload was reduced over the holiday, partly as a result of the official closure of about 50 beds because of nursing shortage. At Northampton Christmas Day and Boxing Day showed a marked decrease in cases counterbalanced by a greater than average number of orthopaedic emergencies over the weekends around Christmas. Of the 21 Saturday trauma patients recorded at Northampton no fewer than 15 occurred on the two Saturdays around Christmas.

Inclusion of the Christmas period in the 1978 survey has not affected the overall pattern at Alder Hey, whilst at The London it has served to limit the increase in average daily service time. To exclude the holiday period would accentuate the difference between the two surveys.

The pattern of work throughout the week at Northampton (with a peak at weekends) was similar during the holiday and non-holiday periods and inclusion of the holiday period in the survey has probably had little effect on the overall sample.

Pattern of work over 24 h

In all three hospitals, in both surveys, the overall pattern of work throughout the day was similar. The pattern seen at The London was typical (fig. 1). There was a little activity in the small hours, a rapid increase around 9.00 a.m. followed by a sustained increase through the day until a peak around 17.00–18.00 h. Thereafter work declined to its lowest level around 03.00 h.

Distribution of work among grades of staff

The grade of anaesthetist treating the patient is shown against the grade thought suitable in figure 2.

The patients represented within the diagonal boxes are those considered to have been attended by an anaesthetist of suitable grade. There has been a reduction in the number of patients to the left of the diagonal at all three hospitals when compared with 1967, and on this basis the service can be said to have improved. A breakdown of the distribution of work between grades of staff is also set out in figure 2.

The urgent work

One important factor which emerged in 1967 was the effect on the service as a whole of dealing with urgent cases.

Any attempt to provide effective service for patients whose maximum tolerable delay is only a small proportion of the average service time is expensive in staffing terms. An increase in the more urgent classes of work therefore has a disproportionate effect on either the staffing needs or the standards of service, or both.

Figure 3 shows, for each hospital, how the total amount of work has changed between the 1967 and 1978–79 samples, and how these different totals were also differently apportioned in terms of urgency. Table III shows the numerical detail.

It will be seen that in all three hospitals a considerable increase of category II work occurred. In table III and figure 3 the priority stated by the person requesting the service has been used, since the serving anaesthetist has to respond as requested, not as he perhaps later finds appropriate. In fact the priority stated by the

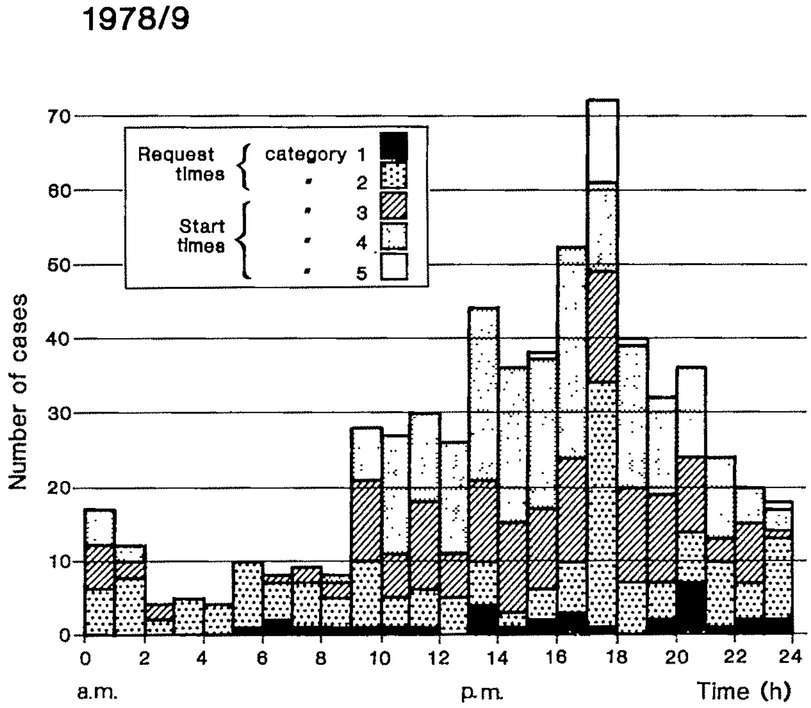

FIG. 1. The hourly distribution of requests for service in categories 1 and 2 and start times for categories 3, 4 and 5 over the whole survey at The London Hospital in 1978–79.

GRADE SUITABLE

GRADE ACTING

LONDON

1967

	1	3	4	5	6	
1	20	1	2	5		7.1
3		8	16	8	3	8.8
4	2	2	167	14	2	46.8
5			11	78	3	23.1
6				8	48	14.2

94.1

1978

	1	3	4	5	
1	8	2	6	2	3.0
3		34	50	11	15.8
4			247		47.3
5			13	189	33.7

97.8

LIVERPOOL

1967

	1	7	8	9	
1	16	13	14	10	13.8
7		10	14	16	10.4
8		11	60	88	41.5
9	1	4	48	78	34.3

83.4

1978

	1	8	9	
1	8	3		4.9
8		1		18.7
9	1	1	170	76.4

99.1

NORTHAMPTON

1967

	1	4	5	
1	18	11	10	8.6
4		74	113	41.0
5		31	199	50.4

93.1

1978

	1	2	3	4	5	
1	9			1	3	2.6
2				1		0.2
3			1	36	4	8.3
4				110	14	25.2
5				28	285	63.6

94.3

KEY.:

1 Consultant
2 Senior Hospital Medical Officer
3 Senior Registrar
4 Registrar
5 Senior House Officer
6 House Officer
7 Senior Assistant - more than one year paediatric experience
8 Assistant - more than six months paediatric experience
9 Junior Assistant - less than six months paediatric experience

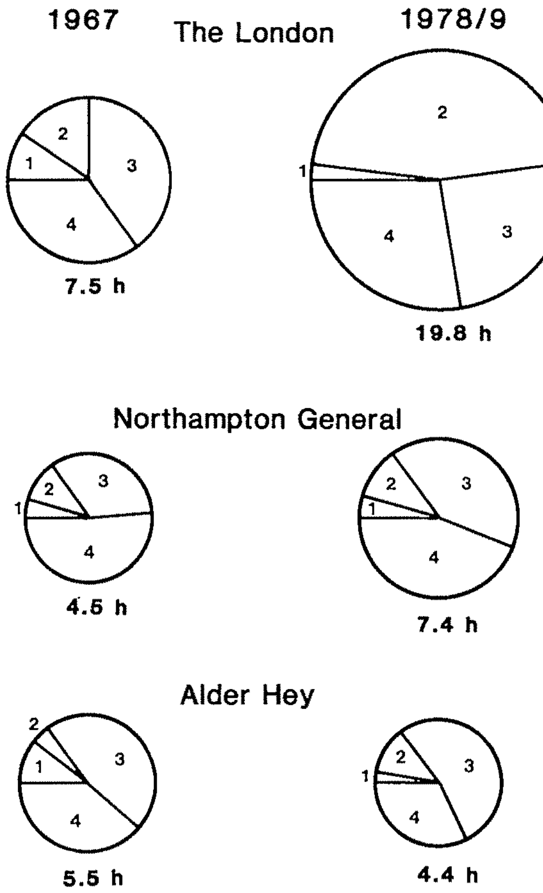

FIG. 3. Between-survey comparison of the proportion of time spent on each of the emergency categories. Category 1 = immediate, 2 = within 15 min, 3 = within 90 min, 4 = within a few hours.

requesting person agrees very well (91–96%) with that assessed by the responding anaesthetist, in both surveys and all three hospitals.

DISCUSSION

The striking difference between the two surveys, a decade apart, is the overall increase in emergency work at The London and Northampton.

Northampton is an expanding "New Town" and the hospital now serves the northern half of the entirely new Milton Keynes in addition to Northampton. It is tempting to assume, therefore, that the increased workload there is a result of population expansion. Further analyses of population data do not support this assumption, however.

In 1966 the population of Northamptonshire was 428 000 and 9 years later it was 505 000. This is equivalent to a rate of increase of 1.9% per annum compound. Over the 11 years between the two samples the workload increased to an extent equivalent to 5.1% per annum compound. Even allowing for the facts that the less rapidly growing northern part of the county is served by the neighbouring Kettering District General Hospital, that the age and sex structure of incoming population fails to match that of the existing population, and that no one catchment population can be stated for all acute specialties, it is clear that an increase in demand has occurred per head of population served.

In the case of The London, acting as a district general hospital for an inner city district, but also as a hospital of special referral for the region and even beyond, it is not possible to make precise estimates of the population served. Neighbouring hospitals in East London have closed, partly reflecting decreasing inner city population, but also increasing the population served by The

TABLE III. *Details of changes in total amount of work and categories of priority of work (figures in parentheses refer to 1967)*

	The London		Northampton		Alder Hey	
Priority	Daily requests	Daily workload (h)	Daily requests	Daily workload (h)	Daily requests	Daily workload (h)
1	0.8 (1.1)	0.36 (0.8)	0.6 (0.4)	0.3 (0.2)	0.2 (0.86)	0.1 (0.6)
2	3.9 (0.96)	9.1 (1.1)	0.5 (0.7)	0.7 (0.4)	0.5 (0.27)	0.5 (0.2)
3	3.7 (2.0)	4.8 (3.0)	3.2 (2.1)	3.1 (1.6)	2.6 (2.4)	2.4 (2.5)
4	5.2 (3.0)	5.5 (2.6)	4.8 (4.8)	3.3 (2.3)	2.1 (3.3)	1.5 (2.2)

FIG. 2. Number and proportion of requests dealt with by each grade at each hospital for both surveys, and grade performing the service compared with the grade subsequently thought suitable.

London in its district general hospital capacity. The inclusion of Mile End Hospital in the London Hospital district has increased the patient population, but in fact only accounted for 13% of the overall emergency workload in 1978, and this has been partly offset by the transfer of Queen Mary's Maternity Home at Hampstead to another health district. Although unable to give precise population figures, we have no doubt that there is no credible alteration in population served that would alone account for the 248% increase in workload over 11 years.

In the case of Alder Hey, the catchment population is determined by age and will be rapidly and considerably affected by the birth rate over the previous few years. Whilst Alder Hey, like The London, is a hospital of special referral over a large area, its workload must be affected by the local birth rate. Between 1967 and 1978 the birth rate in the city of Liverpool declined to less than half but, as elsewhere, the birth rate in Liverpool has now started to increase again. Analysis of theatre records from July 1967 to June 1968 and from July 1978 to June 1979 show that in 1967–68 there was no significant quarterly variation ($P = 0.35$) in the number of emergencies at Alder Hey with an average of 480 per quarter, but in 1978–79 there were only 448 emergencies during the 3 months of October to December, compared with an average quarterly figure of 528. Seasonal factors and non-comparable survey periods may therefore have played a large part in the apparent reduction of emergency workload at Alder Hey during the 1978–79 survey. We have no doubt that in all three hospitals the past decade has seen a substantial increase in demand for emergency anaesthetic service per head of population served.

The data we have do not permit quantification of this increase. Because of the geographically discrete catchment area, the Northampton data are probably the best indicators of the order of the increase, which appears to be a few per cent per annum compound. If this is so, and such a rate of increase is sustained, the staffing implications within a consultant career of, say, 30 years will be marked.

In all three hospitals a considerable increase in ITU work is apparent. In the case of The London this increase was enormous. The *extra* work in the ITU at The London exceeds the total emergency work of *all* kinds in 1967.

There are several possible reasons for this change: first, availability of ITU facilities for patients recovering from surgery leads to greater willingness amongst surgeons to tackle difficult cases. Second, awareness of what an ITU has to offer is now widespread amongst doctors, nurses and the general public. Third, the increasing use of high technology medicine in treating the sickest patients is only possible by concentration of these expensive resources in one place. Increasing experience of the benefits has widened the indications for high technology medicine. Fourth, once an ITU is opened the indications and justification for keeping the very sick in ordinary wards diminishes or perhaps disappears. This has been regretted on the grounds that the training in the care of the critically ill in ordinary wards, of nurses mostly, but of doctors too, has been weakened. This is probably so, but there can be no case for putting patients at risk in order to spread the training more evenly. Over the period between surveys admissions to the six-bedded ITU at The London increased from about 16 per month to more than 40 per month with the largest increase being in postoperative patients. In the autumn of 1978, bed occupancy was about 70%, compared with only 40% in 1967. At the same time average duration of stay had reduced from more than 100 h to just over 60 h.

It is likely that such an increased turnover would account for much of the increase in anaesthetic service time, although we would hope that there have also been improvements in medical practice which might account for some of the extra workload. Whether such an extra burden of work has benefited patients is difficult to prove, since it is impossible to know what would have occurred without intensive therapy. Mortality rates have not changed significantly over the years, the overall ITU mortality rate being 13.6% between the years 1965 and 1980. Whether the total amount of medical involvement has altered cannot be discovered from these data. That the total amount of anaesthetic involvement has increased is clear enough.

If our estimate of a 2 or 3% per annum increase in demand for anaesthetic emergency service per head of population is correct, then it is important for future planning to make an assessment as to whether such an increase will be sustained. The findings here presented suggest that the most important single area to consider is intensive therapy.

Mathematical analysis of an emergency service system

Taylor and others (1969a, c) described the use of queuing theory to examine an emergency anaesthetic service. The mathematical formulation permits application in principle to any emergency system. The much more powerful computing techniques available in 1979 permitted a refinement in the method of analysis. The details are set out in the Appendix.

The refinement slightly improves, and therefore slightly alters, the prediction of the system being occupied with one, two or more cases. The overall results are virtually the same by either method of calculation. Many of the results are of local interest only and will not therefore be reported here. Two aspects are of perhaps wider interest. They are: the implications of an increase in workload; and the question of whether separate provision should be made for urgent work.

Implications of an increased workload

Whilst the considerable increase in work at The London is greater than that seen at Northampton, it is possible that The London, with its teaching and research obligations, particularly in regard to growing areas of knowledge, is untypical. Similarly, the children's hospital with its high degree of specialization and a catchment population immediately responsive to changes in birth rate is also untypical.

Northampton General is probably reasonably representative of many district hospitals, except for the rapid increase in catchment population over the decade. There is little question that the emergency workload here has increased and several factors including population growth, changed surgical practice, and new services such as obstetric analgesia are important.

The implications of the 80% increase in service time need to be examined.

In Northampton with two on-call anaesthetists provided on site, the possibilities to be considered are: that neither is working, that one is working or that both are working. In queuing terms, what we are interested in are the probabilities of there being none, one or two (or more) patients in the system. These probabilities may be conveniently represented by P_0, P_1 and P_2 respectively. As was described by Taylor and others (1969c), in principle queuing theory allows one to predict these probabilities from knowledge of the workload, and both in 1967 and in 1978–79 the actual findings were reasonably close to these predictions.

In figure 4 P_0, P_1 and P_2 have been plotted against time over an average 24 h. The implications of the 1967 workload are shown as a dotted line, of the 1978–79 as a continuous line. Lines CD and C′ D′ lie along a probability of 1% and tell us that, whereas in 1967 there were about 8 h per day when the probability of finding at least one free person was at least 99%, by 1978–79 this had shrunk to about 4 h. The implications for the patient need no explanation.

The implication of the increased workload for staff is exemplified by the lines AB, A′B′. These lines lie along a probability of 90% and tell us that, whereas in 1967 there was a period of about 8 h when the probability of both on-call people being able to sleep was at least 90%, by 1978–79 this had shrunk to about 3 h. It is unreasonable to expect that an anaesthetist who is on call 2 nights per week is also able to undertake responsible work next day. The increased workload recorded in this survey may indeed have adverse effects on both patient and anaesthetist.

Should separate provision be made for urgent cases?

Taylor and others (1969d) suggested that the answer to this question is "No". Separate provision for urgent work seems attractive. In practice such provision has to be made from finite resources and a detailed examination of the 1967 data suggested that the less urgent cases would have to pay a high price for a modest improvement in the service to more urgent cases. It seems desirable to examine this again, in particular for The London Hospital where there has been an enormous increase of ITU emergency work as previously described. If there is a case to be made for separate provision of services for category one and two patients, then it would, we believe, emerge from the data at The London.

In 1967 Taylor and colleagues (1969d) suggested that a reasonable and attainable objective was a service in which not more than 5% of category 1 patients wait more than 3 min, not more than 2.5% of patients in either category 1 or category 2 wait more than 15 min, and not more than 1% of patients in the first three categories wait more than 120 min. These are really three separate criteria, but for the sort of workloads

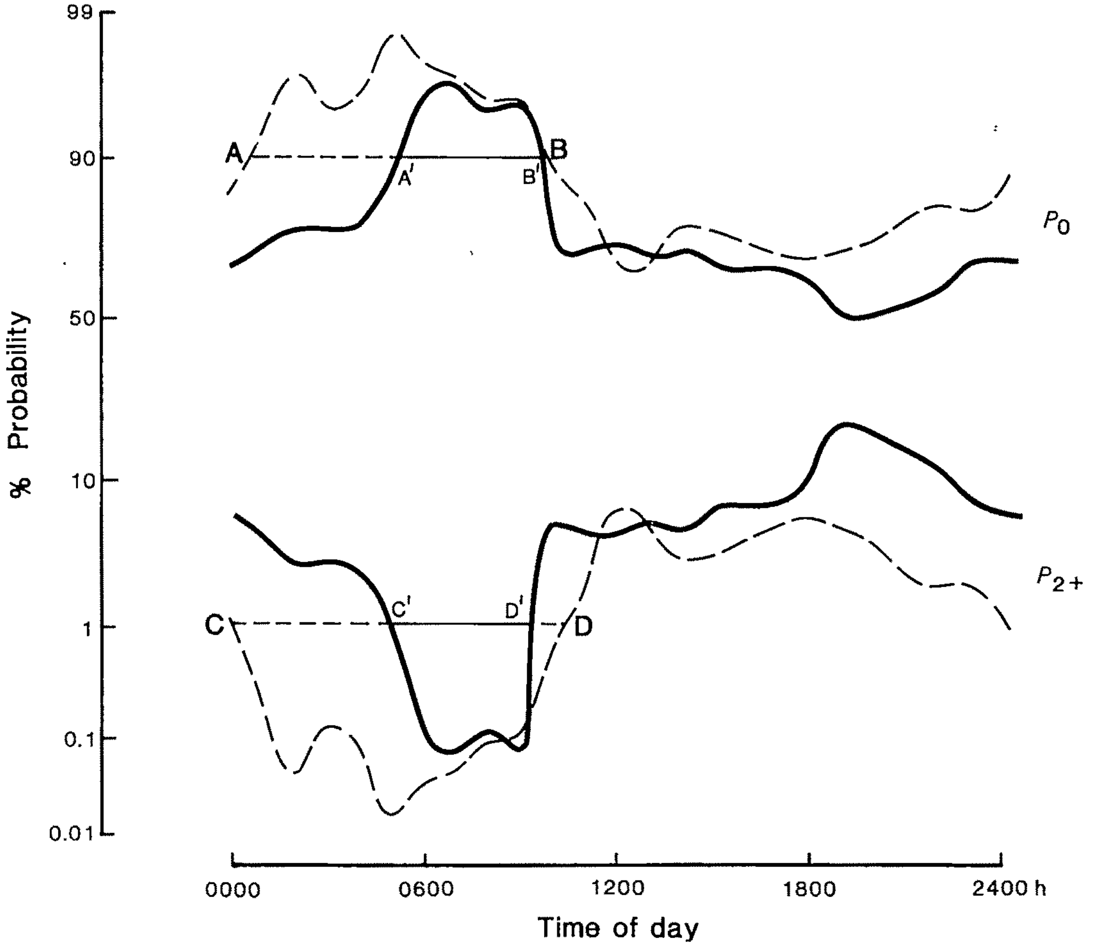

FIG. 4. Daily pattern of changing probabilities of the anaesthetic emergency system at Northampton being in one of two states: P_0—probability that there is no patient in the system and both on-call people are free; P_2—probability that there are two patients or more in the system and that both on-call people are occupied. The curves are derived by theoretical calculation from actual data. Lines A–B and A'B' represent the period of time in 1967 and 1978–79 respectively when both on-call people had a high probability (90%) of being able to sleep. Lines C–D and C'D' represent the period of time in 1967 and 1978–79 respectively when there was a high probability (99%) of finding at least one free person.

observed have very similar staffing implications and will be collectively referred to as "the standard of service".

A computer model was constructed using the data of The London Hospital. It could be run in two ways:

(a) *Pooled resources.* The assumption was made that all on-call staff are pooled and deal with any case of whatever priority. From the actual workload for each hour, an hourly estimate was made of the number of on-call staff needed to maintain the standard of service. The workload varies, and therefore this staffing need varies. It is shown as a dotted line in figure 5.

(b) *Segregated resources.* The assumption is made that there are two separate staffs. One staff deals with category 1 and 2 patients and, given the workload falling into these categories, the size of this staff is implied by the standard of service. The other staff deals with the rest of the work, and again the standard of service taken with the varying workload implies the numbers needed. This is shown as a solid line, figure 5.

These findings fail to support the suggestion

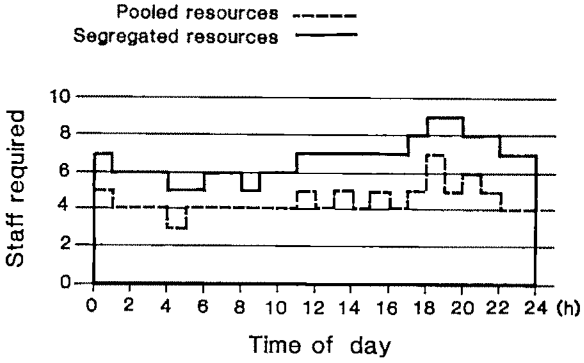

FIG. 5. Staff required to meet the criteria that: (1) not more than 5% of category 1 patients wait more than 3 min; (2) not more than 2.5% of category 1 and 2 patients wait more than 15 min; (3) not more than 1% of category 1, 2 and 3 patients wait more than 120 min over the average day's workload as found at The London in 1978–79. The dashed line --- indicates the staffing levels required when all staff are available for all patients, and the solid line —— indicates the levels required when staff are reserved for priority 1 and 2 patients.

that separate staffing of the more urgent work is an efficient way of deploying staff or serving patients.

In conclusion, therefore, there have been great changes in the amount and type of anaesthetic emergency service since the late 1960's. Intensive therapy service has increased enormously at all three hospitals. The implications for service provision are many, but the first requirement is to document the changes. There is a need for much more data of this type if we are to plan effectively the future of our specialty.

APPENDIX

In 1969 the computing power available did not permit any better allowance for the altering workload of the average day than to make running averages for each hour in turn.

In 1979 it was possible to solve the queuing equations in spite of the fact that the queue never reaches equilibrium.

Let P_n represent the probability of there being n cases in the system. Clearly n must be a whole number, can be zero, and cannot be negative. Let λ be the arrival rate, and let μ be the service rate. λ is equal to 1/mean time between arrivals, so that it is measured in cases arising per unit time. μ is 1/mean service time, so that it is measured in patients dealt with per unit of time.

As an example, consider a system with two servers:

A system in state 0 (no cases) can only go in one jump to state 1 (one case) and can only arise in one jump from state 1. There is, of course, no state -1. The likelihood of a transition from state 0 to state 1 is the product of the arrival rate, λ, and the likelihood of the system actually being in state 0, which is P_0. The likelihood of a transition from state 1 to state 0 is the product of the service rate, μ, and the likelihood of the system being state 1 in the first place, P_1.

The balance between the two flows, into and out of state 0, determines how the probability of being in state 0 alters with time. This can be written.

$$\frac{dP_0}{dt} = -\lambda P_0 + \mu P_1$$

Two transitions out of state 1 are possible: one to state 0 by virtue of completion of service given by μP_1, the other to state 2 because of an arrival given by λP_1.

Two transitions into state 1 are possible. One is from state 0 with probability λP_0. The other is from state 2. In a two-server system, the rate of movement out of state 2 by completion of service is doubled because there are two servers and both must be serving when there are two cases. So this flow is given by $2\mu P_2$, not μP_2.

The balance for state 1 can be written:

$$\frac{dP_1}{dt} = -(\lambda + \mu)P_1 + \lambda P_0 + 2\mu P_2$$

The transitions out of states 3, 4, 5 and so on are not $3\mu P_3, 4\mu P_4 \ldots$, but $2\mu P_3 \cdot 2\mu P_4 \ldots$ because, although there are 3, 4 ... cases in the system, there are only two servers, so only two of the 3, 4 ... are being served.

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L'ANESTHESIE DANS UN SERVICE D'URGENCE, ETUDIEE DANS TROIS HOPITAUX—UNE DECADE DE CHANGEMENT

RESUME

Les résultats d'une étude de 6 semaines de travail anesthésique en urgence, faite en 1978, sont comparés à ceux d'une même étude faite en 1967. Le travail porte sur trois hôpitaux, un hôpital universitaire, un centre hospitalier régional et un hôpital spécialisé en pédiatrie. Dans les trois hôpitaux la

quantité de travail de'urgence a augmenté proportionnellement à la population concernée, la plupart de ce surcroit de travail étant représentée par des soins intensifs. Les conséquences de ce fait, pour les besoins d'un département d'anesthésie, sont discutées.

ANÄSTHESIOLOGISCHER NOTFALLDIENST AN DREI KRANKENHÄUSERN: ERFAHRUNGSBERICHT NACH EINEM 10-JAHRIGEN INTERVAL

ZUSAMMENFASSUNG

Die Ergebnisse einer 6-wöchigen Übersicht eines Anästhesie-Notfalldienstes aus dem Jahr 1978 wurden mit jenen Erfahrungen aus dem Jahr 1967 verglichen. Drei Krankenhäuser wurden ausgewählt, ein Fortbildungs-Lehrkrankenhaus, ein Krankenhaus der Versorgungsstufe I und eine Spezial-Kinderklinik. Es zeigte sich, dass in allen drei Krankenhäusern, bei einer allgemeinen Zunahme der medizinischen Leistungen für die Bevölkerung, die Notfallmedizin sogar überdurchschnittlich zunahm. Hierbei nimmt die Intensivmedizin den breitesten Raum ein. Die Konsequenz der Versorgung im Anästhesie-Dienst wird diskutiert.

SERVICIOS DE EMERGENCIA PARA LA ANESTESIA EN TRES HOSPITALES–UNA DECADA DE CAMBIOS

SUMARIO

Se llevó a cabo una comparación de los resultados de una encuesta de 6 semanas sobre trabajos anestéticos de emergencia finalizada en 1978 con los de una encuesta previa de 1967. Se sacaron muestras en tres hospitales, un hospital docente para estudiantes universitarios no licenciados, un hospital general de distrito y un hospital pediátrico especializado. En los tres hospitales, la carga de trabajos de emergencia aumentó en relación con la población atendida, contando la terapia intensiva por la mayor parte de la demanda adicional. Se discuten de las consecuencias en cuanto a provisión de un servicio anestético.

Br. J. Anaesth. (1982), 54, 279

PATIENT ADMINISTRATION OF I.V. BUPRENORPHINE FOR POSTOPERATIVE PAIN RELIEF USING THE "CARDIFF" DEMAND ANALGESIA APPARATUS

J. M. Gibbs, H. D. Johnson and F. M. Davis

SUMMARY

In 51 patients undergoing elective abdominal surgery, analgesia was provided for the first 24 h after surgery by bolus injections of buprenorphine 0.1 or 0.2 mg given i.v. on patient demand using a patient-operated syringe driver (the "Cardiff" palliator). Excellent analgesia was reported by 47 patients. Four elderly patients had difficulty in operating the demand apparatus. In two other patients, clinically significant ventilatory depression necessitated abandoning the trial. Although there was a high degree of patient and staff acceptance of the method, the potential for ventilatory depression emphasizes the need for close observation of patients receiving i.v. opioids by this technique.

There seems to be general agreement that the traditional technique for the provision of postoperative analgesia by intermittent i.m. injection of an opioid drug does not meet the needs of some patients. Various alternative techniques for the administration of opioids after surgery have been investigated. Sechzer (1968) and Forrest, Smethurst and Kienitz (1970) described techniques for self-administration of i.v. analgesics. Keeri-Szanto (1971) reported the use of a patient-activated "demand" apparatus which allowed for the administration of a predetermined aliquot of an opioid drug when activated by the patient. Use of a similar apparatus was reported by Evans and others (1976) and Chakravarty and others (1979).

The present study was designed to evaluate this device (the Cardiff Palliator) for the first 24 h after operation in a group of patients undergoing abdominal surgery. Buprenorphine (Temgesic) was used because its long duration of action should have resulted in fewer demands for analgesia in the early period after operation when compared with a shorter acting drug. It was hoped that fewer demands would improve patient acceptance. Two doses of buprenorphine were chosen to determine if analgesic requirements were similar at both doses.

METHODS

The study was approved by the hospital ethics committee. Sixty-one patients presenting for elective abdominal surgery were included in the study. At a preoperative interview, the objectives of the study were explained and informed consent obtained. The patients were given the opportunity to practise with the demand button, which required two consecutive pressures within a period of 1 s to activate the syringe pump. The patients were divided into two groups, one receiving doses of buprenorphine 0.1 mg (group A) while the other received 0.2 mg (group B). Premedication was with oral diazepam 10 mg or lorazepam 2.5 mg. The anaesthetic sequence comprised thiopentone, nitrous oxide, oxygen and halothane with a non-depolarizing muscle relaxant. On arrival in the recovery room after surgery the demand apparatus was connected via a Y connection to the patient's i.v. infusion. A 20-ml syringe was filled with buprenorphine 0.1 or 0.2 mg ml^{-1} in 0.9% sodium chloride. The control mechanism was set to deliver aliquots of 1 ml on each patient demand. Care was taken to see that the patient's i.v. infusion was properly maintained throughout the study period. When the patient complained of pain on wakening from anaesthesia, the first aliquot of analgesic was administered by the recovery ward staff. The time was taken as the commencement of the study. Thereafter the patient was responsible for his or her own analgesia by a double pressure on the demand button as described above. The apparatus was set to prevent a further aliquot of

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buprenorphine being administered for a period of 15 min after a "successful" demand, to allow time for an analgesic effect to develop and to reduce the likelihood of drug overdose. The times at which successful demands were made were recorded on a chart recorder activated by the demand apparatus.

The demand apparatus was used to provide analgesia for 24 h from administration of the first dose of buprenorphine. During the first 6 h, the patients were observed intensively in the recovery ward by the second author. Pain was reported by each patient as *none*, *slight*, *moderate* or *severe* (0, 1, 2 or 3). The degree of sedation was assessed by the observer as none, slightly drowsy, drowsy or asleep (0, 1, 2 or 3). Heart rate, arterial pressure and respiratory rate were recorded together with the occurrence of side-effects such as nausea, vomiting and sweating. These observations were made at time zero, when the first dose of analgesic was given and then at intervals of 30 min, 60 min, 90 min and 2, 3, 4, 5 and 6 h. The patients were then returned to the ward with the demand apparatus. After the study period, sublingual buprenorphine was used to provide analgesia. The patients were interviewed again 48 h from the conclusion of this study to determine their reactions to the technique and to evaluate the subsequent trial of analgesia using buprenorphine tablets.

RESULTS

Sixty-one patients were studied in the trial. Ten of these failed to complete the full programme: four patients received alternative analgesic medication in error during the trial period; two patients developed excessive ventilatory depression as detailed below; results from two patients were lost because the chart recorder failed to annotate all demands, and in two patients the demand apparatus did not function properly. This was not an inherent fault, but resulted from an initial attempt to modify (incorrectly) the chart recorder output of the apparatus. Once this had been recognized, the apparatus functioned without fault.

TABLE I. *Details of groups A and B*

	Group A	Group B
Buprenorphine dose (mg)	0.1	0.2
Operative procedure		
Cholecystectomy	22	14
Bowel resections	3	7
Other	1	4

TABLE II. *Patient group characteristics. Mean values and SD*

	Group A	Group B
Number of patients	26	25
Age (yr)	48±15	45±17
Height (cm)	165±9	166±8
Weight (kg)	69±12	66±16
Body surface area (m^2)	1.74±0.17	1.71±0.22

TABLE III. *Number of demands and total dose of analgesic received. Student's* t *test (two-tailed): *t = 3.240,* P<0.01*; †t = 1.429,* P>0.10*; ‡t = 1.326,* P>0.10

	Group A	Group B
Incremental dose (mg)	0.1	0.2
Demands during study		
Total	264	153
Mean number for each patient*	11	6
SD	7	3
Range	3–33	1–14
Dose during study in relation to weight ($mg\,kg^{-1}$)		
Mean†	0.016	0.020
SD	0.010	0.012
Range	0.004–0.044	0.003–0.054
Dose during study in relation to body surface area ($mg\,m^{-2}$)		
Mean‡	0.61	0.76
SD	0.41	0.38
Range	0.16–2.06	0.11–1.76

The types of operative procedure are shown in table I. Group A comprised 26 patients and group B comprised 25 with age and physical characteristics as set out in table II. The number of demands and total dose of analgesic received are shown in table III. There was a wide range in the number of demands, patients in group A making a significantly greater number ($P<0.01$) than those in group B. The patients in group B needed a greater mean dose of analgesic, although the difference between groups did not reach statistical significance (table III), whichever way the dose is expressed. Figure 1 shows the times (in relation to time zero) at which demands were made during the 24 h of the study. The highest frequency of

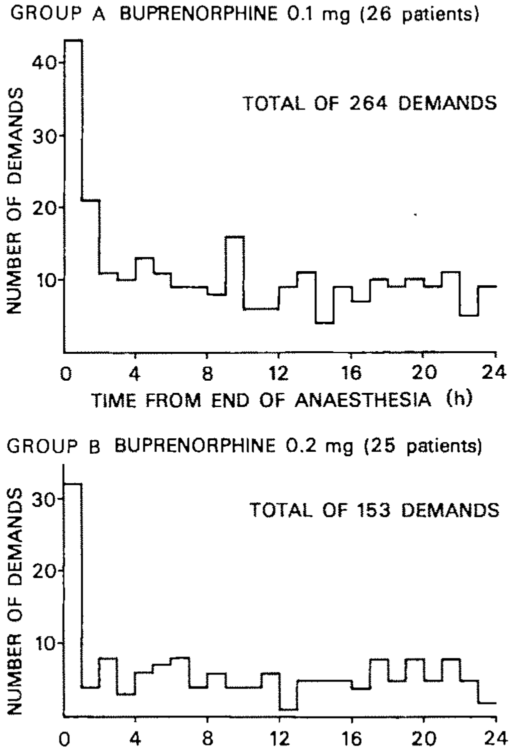

FIG. 1. Frequency of demands for analgesia.

demands was in the first 2 h of the study. Thereafter demand frequency was distributed fairly uniformly.

Results of cardiovascular measurements during the initial 6 h are shown in figure 2. Changes in arterial pressure and heart rate were minimal with no apparent change related to drug administration. On the other hand, both doses of buprenorphine were associated with slowing of the respiratory rate (fig. 3). These changes were statistically significant at the times indicated when compared with the rate at the time of initial drug administration.

At time zero, pain was arbitrarily graded as severe because, during the period of waking from anaesthesia, the patients were unable to give an adequate description of their pain state. Group B was associated with a more rapid change in the pain score, statistically significant at 30 min and 1 h by analysis of variance (fig. 4). In both groups pain was reported (as an average) *slight* during the intensive observation period. At the same time, sedation scoring showed slight to moderate drowsiness in both groups. If a patient was too drowsy to reply when asked about pain, this was taken as signifying *no pain*.

Other side-effects of buprenorphine observed during the study included marked slowing of respiratory rate in two patients. Arterial blood-gas measurements confirmed significant hypercarbia ($P\text{CO}_2$ 8.5 kPa and 9.1 kPa). This was treated by an infusion of doxapram 1.0 mg ml^{-1} over periods of 3 and 5 h respectively. In one of these patients an aliquot of analgesic was administered by an attendant, contrary to the plan of study. In the other, the ventilatory depression was associated with five increments of buprenorphine 0.1 mg taken by the patient over a period of 5 h. Nausea on sitting up in bed was reported by 32 patients at some time during the 24 h of the trial. Eleven patients in group A and nine patients in group B received an antiemetic (metoclopramide

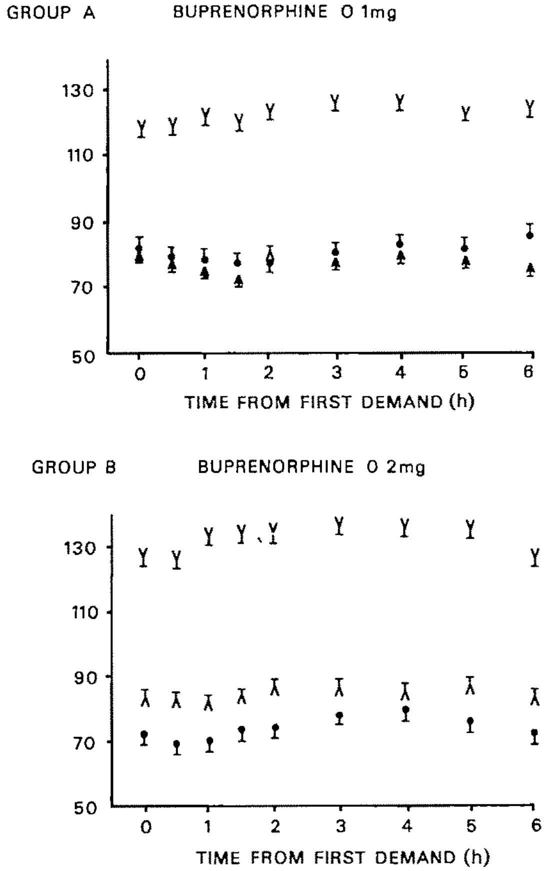

FIG. 2. Cardiovascular changes during intensive observation period. Vertical axis: arterial pressure (mmHg) and heart rate (beat min^{-1}). Vertical bars = SEM. v = systolic; ∧ = diastolic; ● = heart rate.

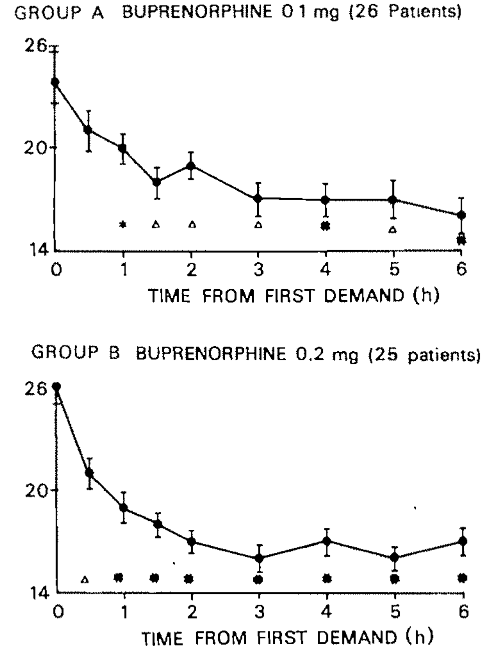

FIG. 3. Respiratory frequency during intensive observation period (vertical axis, b.p.m.). Rate at time of initial observation compared with subsequent rates (two-tailed Student's *t* test). $*P<0.05$; $\triangle P<0.01$; $\#P<0.001$. Values are mean ± SEM.

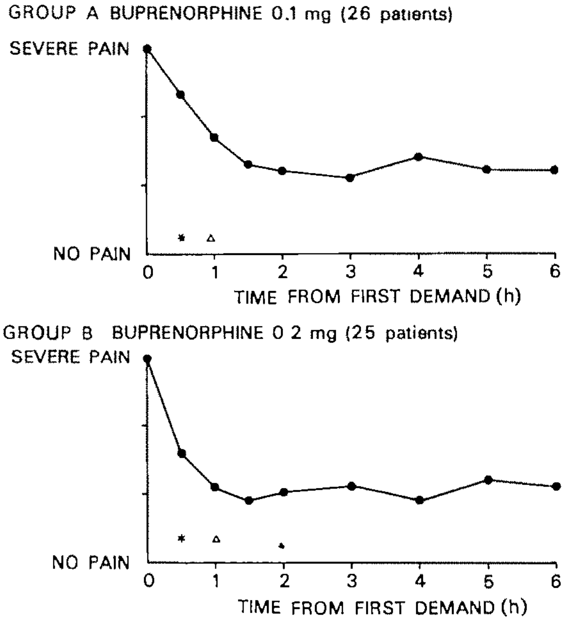

FIG. 4. Mean pain scores during the intensive observation period. At 30 min (*) and 1 h (△) pain scores were significantly different by analysis of variance. $*F = 9.02$, $P = 0.004$; $\triangle F = 6.90$; $P = 0.012$. For this analysis, one value was omitted (chosen at random) from group A to make group sizes identical.

or prochlorperazine) during the trial. Nausea or vomiting was not severe enough to warrant discontinuation of the trial in any case.

At the post-study interview, each patient was asked whether he was satisfied with the analgesia provided during the demand study. Forty-one patients reported satisfactory pain relief. Four experienced difficulties in operating the demand button. Their ages were 67, 74, 59 and 71 yr. Six patients were concerned at the nausea associated with drug administration, although analgesia was satisfactory. There was a high degree of acceptance of the analgesia technique by nursing staff.

DISCUSSION

Buprenorphine administered i.v. on patient demand produced excellent analgesia in the first 24 h after abdominal surgery in 47 of 51 patients. Dissatisfaction with the method related to difficulties in operating the demand button (in elderly patients) or to drug-related nausea. Staff acceptance was high. A wide variability of dose of buprenorphine was observed, in keeping with earlier studies of i.m. postoperative analgesia (Gibbs and Johnson, 1978, 1980) carried out in this department. Demand analgesia should allow for the needs of different patients and of the same patient at times of varying pain by providing a more flexible regimen of drug administration than would be possible with either intermittent i.m. or i.v. bolus injections or even of continuous i.v. infusion (Sechzer, 1971; Chakravarty et al., 1979; Tamsen et al., 1979; White, Pearce and Norman, 1979).

I.v. drug administration has the potential to cause significant drug-related depression of body functions if an inappropriate dose is administered. Too large a dose might be given for the needs of the patient, there might be a failure of the demand apparatus or demands might be made for analgesic within too short a period of time. The apparatus limits the total dose of analgesic available by the amount of drug in the syringe and rejects a demand made by the patient for a specified time after a successful demand. This was set at 15 min in this study as Kamel and Geddes (1978) suggested that analgesia after i.v. buprenorphine would have occurred within that time. In the two cases of clinically significant ventilatory depression, this requirement was met, although in one the analgesic was not self-administered as required with this technique. The potential for such depression reinforces the need for adequate observation of patients requiring i.v. opioids. A further safeguard would be the incorporation of a pneumograph-based limitation of drug dose by the demand apparatus as advocated by Hull and Sibbald (1981).

Bolus i.v. injections are not likely to provide steady state tissue concentrations of the drug as does an i.v. infusion. However, Tamsen and others (1979) found that individual patient control of drug concentration correlated well with that which would be predicted by a computer in terms of the constancy of blood drug concentration. In addition, blood concentrations of opioid drugs may not accurately reflect their activity at their site of action in the brain stem and spinal cord. Although Stapleton, Austin and Mather (1979) found good correlation between blood concentrations and analgesia for pethidine, Bullingham and others (1980) found a decrease in plasma buprenorphine at 1 h after i.v. drug administration which did not correlate with the observed long duration of effect of the drug. A closer correlation might be found with c.s.f. drug concentrations and Villiger, Boas and Taylor (1981) have shown high values for buprenorphine following an i.v. injection at a time of decreasing plasma concentration. Another consideration with opioid drugs relates to their binding to the opioid receptor. Rance and Dickens (1978) have shown that buprenorphine dissociates extremely slowly from receptor sites in rat brain and it seems likely that this property is responsible for its long duration of action.

The present study showed variations in the number of patient demands, to a greater extent than is likely to be explained on a basis of the pharmacokinetics of buprenorphine if there is a threshold value for adequate analgesia as suggested by Stapleton, Austin and Mather (1979) in their studies using pethidine. The present study did demonstrate a significantly greater number of demands made by patients receiving the smaller incremental dose of buprenorphine, suggesting that there may be a dose–response effect, although this could not be defined precisely. In their study of demand analgesia, Tamsen and colleagues (1979) showed considerable inter-patient variation in pethidine consumption and in mean plasma pethidine concentrations. Other studies have shown similar variability in demand frequency (Evans et al., 1976; Chakravarty et al., 1979; McQuay et al., 1980). Using an anaesthetic technique which established dose requirements for an opioid drug during anaesthesia Keeri-Szanto (1979) identified patients who continued to demand analgesia at the "anaesthetic" rate and another group who made demands at a greater rate than that predicted by their requirements during anaesthesia. The techniques used in the present study do not permit analysis of data in the same way but Keeri-Szanto's identification of two patterns of demand usage might explain some of the variability noted in this and other studies. The present study confirmed the high degree of patient acceptance of demand analgesia reported by others cited in this paper. However, as Egbert and others (1963) showed, a measure of personal attention greatly enhances the treatment of postoperative pain. Hull and Sibbald (1981) described a background maintenance infusion of fentanyl to which demand pulses of this analgesic could be added. The complexity of their system would seem less necessary with a drug such as buprenorphine because of its vastly different pharmacodynamics.

The present study confirms the suitability of demand analgesia for the treatment of postoperative pain after abdominal surgery. Because of the potential for ventilatory depression it is necessary that patients be adequately supervised. The difficulty of reversing ventilatory depression caused by buprenorphine (Orwin, 1977) means that particular care must be exercised.

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AUTOADMINISTRATION INTRAVEINEUSE PAR LES MALADES DE BUPRENORPHINE, ANALGESIQUE POSTOPERATOIRE, A L'AIDE DE L'APPAREIL DIT DE "CARDIFF"

RESUME

Chez 51 patients ayant subi une intervention chirurgicale à froid à l'abdomen, l'analgésie a été entretenue au cours des 24 premières heures suivant l'opération à l'aide d'injections de bols de buprénorphine, à raison de 0,1 ou 0,2 mg, administrées par voie intraveineuse au fur et à mesure que les patients le demandaient, en utilisant un dispositif d'entraînement de la seringue actionné par le patient lui-même (le palliatif de "Cardiff"). Il a été signalé que l'analgésie avait été excellente sur 47 patients. Quatre d'entre eux, parmi les plus âgés, ont eu des difficultés à faire fonctionner le dispositif d'entraînement sur demande, alors que chez deux autres, il a fallu abandonner les essais en raison d'une dépression ventilatoire importante du point de vue clinique. Bien que cette méthode ait été largement appréciée par les patients et par le personnel médical, la possibilité de dépression ventilatoire fait ressortir la nécessité de tenir les patients sous observation étroite lorsqu'ils s'administrent des opiacés par cette méthode.

PATIENTENBEHANDLUNG MIT INTRAVENÖS VERABREICHTEM BUPRENORPHIN ZUR POSTOPERATIVEN SCHMERZLINDERUNG UNTER VERWENDUNG DES VON PATIENTEN BEDIENTEN "CARDIFF"-ANALGESIEAPPARATES

ZUSAMMENFASSUNG

Ein und funfzig Patienten erhielten für die ersten 24 Stunden nach verschiedenen Unterleibsoperationen schmerzlindernde Bolus-Injektionen von intravenös verabreichten 0,1 oder 0,2 mg Buprenorphin, und zwar mit der auf Wunsch von den Patienten bedienten Injektionsanlage, dem "Cardiff"-Palliativ-apparat. Seben und vierzig Patienten meldeten eine hervorragende Wirkung, vier ältere Patienten hatten Schwierigkeiten bei Bedienung des Apparates: bei zwei weiteren Patienten machte eine klinisch signifikante Atemstörung den Abbruch dieses Versuchs erforderlich. Obwohl Patienten und Pflegepersonal in hohem Masse diese Methode akzeptierten, lässt ihr Potential für Atmungsdämpfungen die Notwendigkeit einer sorgfältigen Beobachtung solcher Patienten erkennen, die mit dieser Methode intravenös Opiate erhalten.

ADMINISTRACION DE BUPRENORFINA INTRAVENOSA AL PACIENTE PARA ALIVIAR EL DOLOR POSTOPERATIVO MEDIANTE EL DISPOSITIVO "CARDIFF" DE AUTOADMINISTRACION DE ANALGESIA POR PARTE DEL PROPIO PACIENTE

SUMARIO

Se proveyó analgesia a 51 pacientes sometidos a operación quirúrjica abdominal y facultativa, por espacio de 24 h después de la operación y mediante inyecciones dosificadas de 0,1 mg ó de 0,2 mg de buprenorfina, las cuales se las administraron los propios pacientes según su necesidad, haciendo uso de un accionador de jeringa manejado por el propio paciente (el aliviador "Cardiff"). 47 de los pacientes comunicaron una analgesia excelente. Cuatro pacientes ancianos tuvieron dificultad con el manejo del aparato. En otros dos pacientes, la existencia de una depresión ventilatoria clínicamente significativa, exigió el abandono del experimento. Aunque la aceptación del método por parte del paciente y del personal fue considerable, la posibilidad de que surgan depresiones ventilatorias pone de relieve la necesidad de observar más de cerca a los pacientes que reciben opioides por vía intravenosa mediante este método.

Br. J. Anaesth. (1982), **54**, 285

CONTROLLED COMPARISON OF I.M. MORPHINE AND BUPRENORPHINE FOR ANALGESIA AFTER ABDOMINAL SURGERY

P. J. COOK, I. M. JAMES, K. E. F. HOBBS AND D. R. G. BROWNE

SUMMARY

In a double-blind randomized non-crossover trial 47 patients received either morphine or buprenorphine by regular i.m. injection for 24 h after abdominal surgery. The two drugs were equally effective as analgesics at the doses used. Five in the buprenorphine group and none in the morphine group were excluded because of respiratory depression. Four of these had received opiates during operation. The remainder of the buprenorphine group developed progressively slower respiration rates after 12 h. The results indicate that buprenorphine has a synergistic respiratory depressant effect with fentanyl and phenoperidine and may have a cumulative effect when given regularly on a 6-hourly regimen.

Buprenorphine is a relatively new synthetic opiate analgesic with a chemical structure similar to morphine (Lewis, 1974; Downing, Leary and White, 1977). Published studies indicate that the drug has a high affinity for the opiate receptor with a long duration of action (Downing, Leary and White, 1977; Kay, 1978). Clinical studies have confirmed that its analgesic potency (w/w) is about 30 times that of morphine. Previous studies comparing buprenorphine with morphine i.m. have used ratios 0.6 : 15 mg (1 : 25) and 0.3 : 12.5 mg (1 : 42). The smallest recommended i.m. dose (0.3 mg) has been found to be at least as effective as morphine 10 mg, but has a longer duration of action of 6–18 h (Downing, Leary and White, 1977; Kay, 1978, 1980). Larger doses (1 mg) have been shown to produce miosis for more than 72 h (Jasinski, Pevnick and Griffith, 1978). The drug is also a narcotic antagonist and Jasinski showed that very large doses (8 mg) are capable of blocking the effects of large doses of morphine (up to 120 mg) for more than 30 h.

Only limited pharmacokinetic data are available. In an early unpublished study in man, the elimination half-life of labelled buprenorphine appeared to be more than 12 h and possibly more than 24 h. A recent study using radioimmunoassay found a mean terminal half-life of 3 ± 1.7 (SD) h, but this may be an underestimate since the sampling period was only 3 h (Bullingham et al., 1980).

All published studies on the parenteral use of the drug have involved single doses or multiple doses on demand. The present study was designed to compare the efficacy and side-effects of buprenorphine and morphine following regular i.m. injection in patients recovering from surgery, using an average dose and dose ratio of the two drugs.

METHODS

Forty-seven patients aged 18–70 yr and weighing 40–90 kg who were undergoing abdominal surgery gave informed consent to the trial, which had been approved by the hospital ethics committee. Most patients received diazepam 10 mg orally as premedication, i.v. thiopentone for induction of anaesthesia and nitrous oxide and halothane or trichloroethylene or opiates for maintenance. Additional anaesthesia and analgesia were given according to the anaesthetist's preferences and all drugs administered were recorded.

After operation patients received either buprenorphine 0.3 or 0.45 mg or morphine 10 or 15 mg i.m. (dose ratio 1 : 33) according to weight (less than or greater than 63 kg). The drugs were administered according to a randomized double-blind non-crossover design. The first dose was given when the patient wakened in the recovery room and subsequent doses were given regularly every 6 h for 24 h. The patients were attended by trained nurse observers for 24 h after operation.

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Baseline heart rate, arterial pressure and breathing rate were noted before operation and repeated immediately before each postoperative injection, to give an assessment of the changes present 6 h after each injection. Pain assessments and additional recordings were made before and 1 h after the 6-h and 24-h injections. The amount of pain was assessed independently by the nurse and the patient using a visual analogue scale consisting of a 100-mm line joining the two extremes marked "no pain" (0 mm) and "unbearable pain" (100 mm). All symptoms and side-effects were noted throughout the period of observation. Nausea and vomiting were treated with metoclopramide 10 mg i.m. as necessary. Provision was made for patients to be withdrawn from the study by the doctor in charge of the case or at their own request because of inadequate analgesia, unacceptable side-effects or complications.

RESULTS

Patient comparability

The age, sex and weight distribution and dose per kg body weight were similar in the two groups (table I). The mean buprenorphine : morphine dose ratio was 1 : 36 in the lighter patients and 1 : 33 in the heavier patients. The premedication, anaesthetic induction and maintenance, the neuromuscular blocking drug and the procedures for its antagonism were similar in both groups. Eleven of the morphine group and eight of the buprenorphine group received opiate analgesia during the operation. One patient in the morphine group who received pethidine was given naloxone 0.3 mg at the end of the operation.

TABLE I. *Comparison of groups of pateints randomly receiving either buprenorphine or morphine i.m. Mean values ± SD. *One patient in each group received two drugs*

	Morphine	Buprenorphine
No. of patients (M)	24 (10)	23 (10)
Age (yr)	45 ± 11	48 ± 10
Weight (kg)	63 ± 13	66 ± 8
Dose (μg kg^{-1}) <63 kg	192 ± 14	5.3 ± 04
>63 kg	208 ± 25	6.4 ± 0.4
Type of operation		
Cholecystectomy	18	20
Other laparotomy	2	3
Hernia repair	4	—
Additional opiate analgesia		
Pethidine	5	2
Phenoperidine	4	5
Fentanyl	3	3
Total*	11	9

Side-effects and withdrawals

The frequency of nausea and vomiting was similar in the morphine (seven patients) and buprenorphine (eight patients) groups. One patient in each group developed a chest infection during the trial period.

Six patients in the buprenorphine group and one patient in the morphine group were withdrawn (Fisher's exact test: $P = 0.042$). One patient in each group was withdrawn because of inadequate analgesia and the remaining five patients in the buprenorphine group were withdrawn because of respiratory depression (table II). One in the morphine group developed serious respiratory depression 2.5 h after the end of the trial and received naloxone. Four of the five in the buprenorphine group had received opiate analgesia during the operation. Three of these were withdrawn within 6 h and the remaining patient, who had been noted to have some respiratory depression at 6 h, was withdrawn at 11 h. The patient who had received no previous opiate analgesia was withdrawn at 18 h.

Pain assessment

The results of the nurse observer and patient pain scores are in table III. There was good agreement between the two assessments. Both drugs were associated with a highly significant degree of pain relief with about a 50–60% reduction in pain score recorded 1 h after injection.

Cardiovascular changes

There were no significant differences in respect of systolic and diastolic arterial pressures or the heart rate between the two groups.

Respiratory rate

The respiratory rates before and after operation were similar in the two groups (table IV). Those patients who received opiate analgesia during operation had similar respiratory rates after operation compared with those who did not. The mean respiratory rates in the buprenorphine group were less than those in the morphine group at both 1 h (Anovar: $P = <0.05$) and 6 h (Anovar: $P = <0.005$) after injection. The differences are confirmed if the changes in respiratory rates from

TABLE II. *Withdrawals. All patients received diazepam 10 mg, i.v. thiopentone, nitrous oxide and halothane and either tubocurarine or pancuronium antagonized by neostigmine with atropine. A/B = small/larger analgesic dosage*

Patients	Age and sex	Weight (kg)	Opiate analgesia at operation	Time and reason for withdrawal	Comment
Morphine B26	25 F	69	0	3 h. Pain	Acute pancreatitis
Buprenorphine					
A3	61 F	56	Fentanyl 0.3 mg	1 h. Respiratory depression	
B14	58 F	73	Phenoperidine 4 mg	4½ h. Respiratory depression	Hypotension C.n.s. depression
A7	59 F	63	0	7½ h. Pain	
B22	57 F	65	Fentanyl 0.2 mg	6 h. Respiratory depression	Hypotension C.n.s. depression Respiratory rate 10 b.p.m. Cyanosis
B16	47 M	67	Phenoperidine 1.75 mg	11 h. Respiratory depression	C.n.s. depression. Subsequent chest infection
B3	61 F	70	0	18 h. Respiratory depression	Drowsiness + + at 6 h. Hypotension. C.n.s. depression

TABLE III. Mean pain scores (mm) before, mean difference in scores ± SEM 1 h after the 6-h and 24-h injections (n). Paired t test *$P<0.01$, **$P<0.001$. Differences between groups not significant

	Mean score at 6 h	Mean diff. in score at 7 h	Mean score at 24 h	Mean diff. in score at 25 h
Patient assessment				
Morphine	56 (23)	−29±4**	31 (23)	−15±4*
Buprenorphine	55 (18)	−31±6**	28 (17)	−18±4**
Observer assessment				
Morphine	52 (23)	−36±5**	30 (23)	−19±5**
Buprenorphine	55 (19)	−38±5*	28 (17)	−19±6*

TABLE IV. *Mean respiratory frequency before operation (±SD), 6 h after each postoperative injection and 1 h after the 6-h and 24-h postoperative injections in patients receiving either morphine or buprenorphine i.m. 6-hourly. Difference between treatment groups 6 h after injection:* $P<0.005$ *(analysis of variance); difference between treatment groups 1 h after injection:* $P<0.05$

	Time (h) since last injection	Morphine group		Buprenorphine group	
		n	Mean respiratory freq. (b.p.m.)	*n*	Mean respiratory freq. (b.p.m.)
Before operation	—	24	17.7±1.8	23	18.7±1.9
After operation					
0 h	—	24	22.2±6.4	23	21.5±5.8
6 h	6	23	21.9±4.5	21	18.3±6.0
7 h	1	23	17.7±3.3	18	16.3±5.9
12 h	6	23	20.0±3.1	17	18.8±3.7
18 h	6	23	19.5±2.8	17	17.2±3.7
24 h	6	23	18.1±3.5	17	16.8±4.1
25 h	1	23	16.2±4.0	17	13.4±4.1

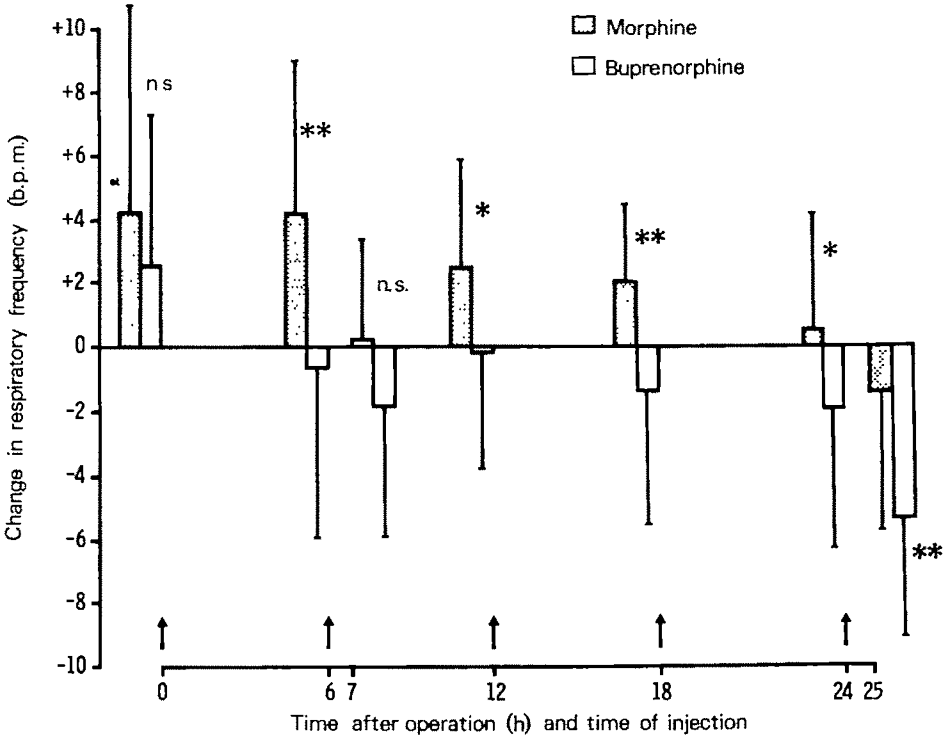

FIG. 1. Change in respiratory frequency (mean ± SD) from preoperative value (table IV) recorded 6 h after each postoperative injection and 1 h after the 6-h and 24-h injections. *Unpaired t test: $*P<0.05$, $**P<0.01$; n.s. = not significant.

the preoperative values are compared in the two groups of patients (fig. 1). The graph shows that both groups had an increased mean respiratory rate immediately after operation; whereas the morphine group returned to the preoperative value by 24 h, the mean respiratory rate in the buprenorphine group continued to decrease to less than the preoperative value after 12 h.

DISCUSSION

The degree of analgesia recorded at 1 and 6 h after injection was similar in the two groups, confirming that the doses used were equipotent. The larger number of withdrawals in the buprenorphine group may have produced an underestimate of its analgesic potency, and the trial design did not allow an accurate comparison of the duration of analgesic effect.

Respiratory frequency increased after operation in both groups of patients, presumably because rapid shallow breathing caused abdominal pain to be less. The significant reduction in respiratory rates 1 h after injection could be explained by both an analgesic effect and a respiratory depressant effect. These two effects can be distinguished by comparison with the basal respiratory frequencies (fig. 1). I.m. buprenorphine given 6-hourly tended to produce very slow respiratory rates and these mean values would probably have been smaller if the five patients with excessive respiratory depression had remained in the trial. Morphine 6-hourly did not depress the mean respiratory rate significantly below the preoperative value. This result indicates that the effect of buprenorphine on respiration is a direct effect not attributable to analgesia alone, and supports previous observations that it has a greater potential than morphine to produce respiratory depression (Orwin et al., 1976a; Baster, Gibbs and Richardson, 1977).

Buprenorphine is a potent opiate antagonist as judged by its ability to produce a withdrawal reaction in dependent primates and its ability to antagonize the effects of morphine in man, and it has been recommended as an effective antagonist following the use of fentanyl during surgery in man (De Castro, 1976). It would be expected to be safe when used after opiates administered during operation in man. However, four of the eight buprenorphine group, but none of the morphine group, who received fentanyl or phenoperidine during operation in this study had evidence of respiratory depression within 6 h (Fisher's exact test: $P = 0.051$). The result suggests that a synergistic respiratory depressant effect can occur with these two opiates but not, apparently, with pethidine.

Fentanyl and phenoperidine have relatively short elimination half-lives—less than 3 h at the doses used (Schleimer et al., 1978; Milne et al., 1980), and will be almost completely eliminated 6–8 h after a dose.

The progressive reduction in mean respiratory rates was seen in the buprenorphine patients even after the peroperative opioid group was excluded. This reduction can only be explained as evidence of plasma accumulation, which would indicate a true plasma half-life of more than 4 h (Wagner, 1967) or receptor accumulation which greatly outlasted the plasma concentration. Serial plasma estimations during regular dosing would answer the question if plasma accumulation occurs. In either case, accumulation would be reduced by extending the dosing interval to 8-hourly and the drug can still provide effective analgesia when given in this way (Kay, 1980).

These observations need further confirmation. Meanwhile caution should be exercised when buprenorphine is given in addition to other opiate analgesia or when the drug is given by regular i.m. injection. This is particularly important when it is remembered that the respiratory depression by the drug is only partially antagonized by naloxone (Orwin et al., 1976b) or doxapam (unpublished) and no other effective antagonist is commercially available.

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COMPARAISON RANDOMISEE DE LA MORPHINE ET DE LA BUPRENORPHINE I.M. POUR L'ANALGESIE APRES CHIRURGIE DE L'ABDOMEN

RESUME

Au cours d'un essai randomisé en double aveugle, sans permutation, 47 patients ont reçu à intervalles réguliers de la morphine ou de la buprénorphine par voie intramusculaire, pendant une période de 24 h, après un acte de chirurgie abdominale. Les deux agents se sont révélés aussi efficaces sur le plan de l'analgésie aux posologies utilisées. Cinq patients du groupe buprénorphine ont dû être exclus à cause d'une dépression respiratoire, ce qui n'est jamais arrivé dans le groupe morphine. Quatre d'entre eux avaient reçu des morphinomimétiques pendant l'intervention. Les autres patients du groupe buprénorphine ont progressivement développé une diminution de leur fréquence respiratoire après 12 h. Les résultats montrent que la buprénorphine a un effet dépresseur respiratoire, synergique de celui du fentanyl et de la phénopéridine et peut avoir un effet cumulatif lorsqu'on l'injecte systématiquement toutes les 6 h.

KONTROLLIERTER VERGLEICH VON MORPHIN UND BUPRENORPHIN I.M. ZUR ANALGESIE NACH ABDOMINAL-CHIRURGISCHEN EINGRIFFEN

ZUSAMMENFASSUNG

In einem randomisierten, Doppel-blind-, nicht cross-over-Versuch erhielten 47 Patienten in den ersten 24 Stunden nach abdominal-chirurgischen Eingriffen entweder Morphin oder Buprenorphin regelmässig als i.m. Injection. Die zwei Pharmaka waren in ihrer analgetischen Wirkung entsprechend ihrer Dosis gleich. Fünf Patienten der Buprenorphin-Gruppe und keiner in der Morphin-Gruppe wurden wegen Atemdepression vom Versuch ausgeschlossen. Vier der Patienten hatten während der Operation Opiate erhalten. Die übrigen der Buprenorphin-Gruppe entwickelten progressiv eine Verlangsamung der Atmung nach 12 Stunden. Diese Ergebnisse zeigen, dass Buprenorphin mit Fentanyl und Phenoperidine eine synergistische Wirkung auf die Atemdepression besitzt und wenn es alle 6 Stunden gegeben wird, sogar eine kumulative wirkung haben dürfte.

COMPARACION CONTROLADA DE LA MORFINA Y DE LA BUPRENORFINA I.M. PARA LA ANALGESIA DESPUES DE CIRUJIA ABDOMINAL

SUMARIO

En un ensayo doble-ciego no-cruzado al azar, se administró a 47 pacientes ya sea morfina ya sea buprenorfina por inyección i.m. regular durante 24 h después de la cirujia abdominal. Ambas substancias fueron igualmente eficaces como analgésicos en las dosis usadas. Cinco pacientes en el grupo de buprenorfina y ninguno en el grupo de morfina feuron excluídos a raíz de una depresión respiratoria. Cuatro de ellos habían recibido opiatos durante la operación. El resto del grupo de buprenorfina desarrolló paulatinamente ritmos de respiración más lentos después de 12 h. Los resultados indican que la buprenorfina posee un efecto depresivo de la respiración sinergistica con el fentanilo y la fenoperidina y puede tener un efecto cumulativo cuando se administra regularmente bajo un regimen horario de 6 h.

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COMPARISON OF FOUR NARCOTIC ANALGESICS FOR EXTRADURAL ANALGESIA

T. A. TORDA AND D. A. PYBUS

SUMMARY

The effectiveness of extradural injections of morphine sulphate 6 mg, methadone 6 mg, pethidine 60 mg and fentanyl 60 µg in relieving pain after operation were compared in 24 patients. The average duration of pain relief following morphine was 12.3 h; methadone 8.7 h, pethidine 6.6 h and fentanyl 5.7 h. There was no significant difference in the efficacy of the four drugs. There were no effects of clinical importance on heart rate, respiratory frequency or arterial pressure, but arterial systolic pressure decreased after morphine and pethidine. Pethidine also caused a statistically significant reduction in diastolic pressure.

The value of extradural opiates and opioids in the relief of postoperative pain is now well established and the use of a number of different drugs, including morphine (Magora et al., 1980), methadone (Bromage, Camporesi and Chestnut, 1980), pethidine (Glynn et al., 1980) and fentanyl (Wolfe and Davies, 1980) has been reported. There has been no report of a controlled comparison of the effects of these drugs. The present study was designed to satisfy this need.

MATERIALS AND METHODS

A "within-patient" controlled trial was approved by the Clinical Trials Committee of our hospital. All the patients in the trial gave informed consent. The participating patients were admitted to the intensive care unit following operations involving extensive abdominal, thoracic or flank incisions.

It seemed probable that the results of the trial could be influenced by the order of administration of the drugs under test: the effectiveness of the first drug administered might be potentiated by the drugs used during anaesthesia or reduced by the intensity of the pain experience in the period immediately after operation. The effect of opiates given later in the postoperative period could apparently be enhanced by the naturally diminishing pain stimulus or be the residual effects of the previously administered opiates. To eliminate such bias, a "latin square" design was adopted so that each of the 24 possible sequences of four drugs was given to one patient.

TABLE I. *Nature of operative procedures and level of extradural puncture in the patients*

Operation	Number	Level of puncture
Thoracotomy	9	T5–6, T6–7
Exploratory laparotomy	5	
Ruptured liver		T10–11
Mesenteric haematoma		T8–9
Pancreatitis		T8–9
Colitis, peritonitis		T10–11
Appendicitis		T10–11
Aortic graft	3	T9–10, T10–11, T11–12
Total cystectomy	3	L2–3
Nephrectomy	2	T10–11
Pyelolithotomy	1	T8–9
R. hemicolectomy	1	T9–10

To obtain 24 complete studies, 34 studies were attempted. Six patients did not require five administrations of an analgesic (five in order that the duration of analgesia produced by the fourth drug could be assessed). In one patient the extradural catheter was not correctly sited (no analgesia from opiate or local anaesthetic). One patient became delirious after operation, probably because of alcohol withdrawal. One patient required positive pressure ventilation for acute respiratory failure which was not related to opiate administration, and one patient was discharged from the unit before completion of the study. In the 24 completed studies, there were nine females and 15 males who ranged in age from 19 to 78 yr and in weight from 60 to 95 kg. The patients were informed of the nature of the study and told to ask

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for analgesia when they experienced pain at rest. They were advised that they would be asked to express a preference for any one of the first four analgesic injections they would be given.

All the patients had opiate premedication and were operated upon under general anaesthesia. Thiopentone induction was followed by maintenance with nitrous oxide in oxygen supplemented by intermittent doses of fentanyl. A neuromuscular blocking drug was given. In eight patients halothane was given also. The three patients who underwent cystectomy had the extradural catheters inserted at the L2–3 interspace, those who underwent abdominal or renal operations had their catheters inserted in one of the thoracic spaces below T8 and in those patients who underwent thoracotomy the catheters were inserted at T5–6 or T6–7. All the catheters were directed cephalad and inserted 2–3 cm into the extradural space.

The four drugs investigated were morphine sulphate 6 mg in a solution containing 0.1% sodium metabisulphite; methadone 6 mg; pethidine 60 mg; and fentanyl 60 µg, all in aqueous solution. Each drug was diluted to 10 ml in sterile normal saline immediately before use.

The first dose of analgesic was administered as soon as the patient complained of pain after the operation—spontaneously or in response to a direct question. Within 45 min all patients obtained effective pain relief. They were instructed to ask for further analgesia as soon as pain at rest returned and were again reminded that they would be asked for their preference for one of the four drugs. Subsequent doses of analgesic were injected on demand. Immediately before and 45–60 min after drug administration the patient's heart rate, respiratory frequency and arterial pressure were recorded. Complaints of nausea or itching and the occurrence of vomiting were also noted. Before the fifth analgesic administration, the patients were asked if they could indicate a preference for any of the four drugs.

The data were analysed in the following manner. The durations of action of the four drugs were compared using the Mann–Whitney Rank Sum test. For comparison of the duration of action of the first, second, third and fourth drugs analysis of variance was used. The values for the vital signs before and after drug administration were tested using the paired *t* test and the significance of any drug preference analysed using the Chi squared distribution.

TABLE II. *Duration of action of the four analgesics and distribution of patient preferences analysed for drug and order of administration*

	Duration of action (h)		
	Mean ± SD	Range	Preferences
Morphine	12.26 ± 7.69	3.00–32.75	6.5
Methadone	8.71 ± 5.89	1.50–27.25	4.0
Pethidine	6.61 ± 3.32	3.00–17.75	3.0
Fentanyl	5.71 ± 3.72	2.00–14.50	1.5
1st drug	8.51 ± 7.52	2.00–27.25	2.0
2nd drug	7.88 ± 6.72	1.50–32.75	2.5
3rd drug	9.06 ± 4.20	3.75–20.00	4.5
4th drug	7.91 ± 4.92	2.00–22.75	6.0

RESULTS

The mean duration of action of morphine was 12.3 h, which was not significantly longer than methadone, 8.7 h. The durations of action of pethidine, 6.6 h, and of fentanyl, 5.7 h, were significantly shorter ($P<0.01$ and $P<0.001$ respectively). The duration for methadone did not differ significantly from pethidine, but was longer acting than fentanyl ($P<0.05$). Pethidine and fentanyl did not differ significantly. The detailed results are contained in table II and shown in figure 1. The analysis of variance did not demonstrate significant differences between the results of

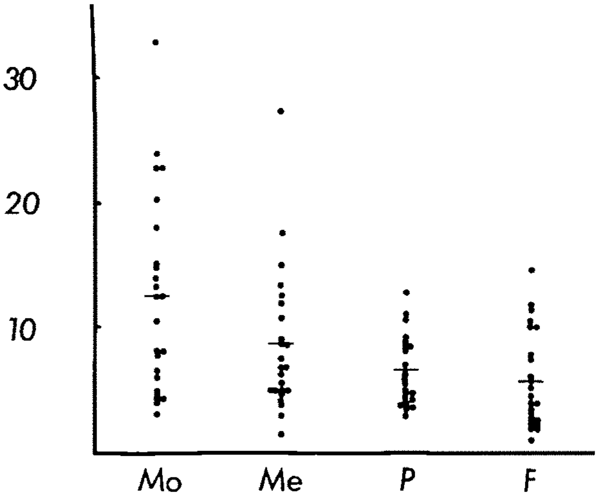

FIG. 1. Scattergram showing the duration of pain relief from the four drugs. Ordinate is time in hours. Mo = morphine, Me = methadone, P = pethidine, F = fentanyl. The bars show the mean duration.

TABLE III. *The effect of the four drugs on heart rate, respiratory frequency and arterial pressure.* *P<0.05; **P<0.01

Drug	Heart rate (beat min^{-1})	Respiratory frequency (b.p.m.)	Systolic pressure (mm Hg)	Diastolic pressure (mm Hg)
Morphine				
Before	97.9±15.9	23.7±3.2	136.8±22.3	73.1±7.3
After	96.2±14.5	21.5±3.8	129.6±17.8*	72.9±9.5
Methadone				
Before	95.4±13.5	24.0±6.5	138.0±25.2	75.8±12.8
After	95.4±13.3	20.9±4.6	132.6±26.3	74.1±12.5
Pethidine				
Before	95.6±12.2	22.9±4.1	133.7±23.7	74.6±10.3
After	95.1±13.0	21.7±4.7	122.7±13.1*	68.8±8.1**
Fentanyl				
Before	98.4±15.8	23.0±5.5	138.3±27.2	74.0±12.7
After	96.3±13.4	21.1±4.0	138.1±24.8	73.5±12.7

the first, second, third or fourth drug administered, nor was there any significance in the distribution of drug preference.

The effects of the four drugs on heart rate, respiratory frequency and arterial pressure are shown in table III. Heart rates were not changed significantly by any of the four drugs. All four drugs reduced respiratory frequency slightly, but none of the changes was statistically significant. The slowest recorded respiratory frequency was 12 b.p.m. In none of the patients was there evidence of depression of respiration which would give cause for concern and there was no statistically significant difference between the mean rates for the four groups.

No patient experienced a decrease in arterial pressure which required treatment, following the administration of any of the drugs. The lowest pressure recorded was 95/50 mm Hg before methadone and this was unaffected by the drug. The decrease in systolic pressure following morphine and pethidine was statistically significant ($P<0.05$) as was the reduction in diastolic pressure following pethidine ($P<0.01$).

Although no serious side-effect was encountered, one patient reported nausea and vomiting following each drug except fentanyl and another became nauseated following morphine and fentanyl. Both these patients responded to treatment with metoclopramide. Three of the patients reported itching following morphine and one of these also developed itching following pethidine. Although promethazine relieved the pruritus, no patient exhibited clinical signs of histamine release. Only 12 of the patients arrived in the Intensive Care Unit without a bladder catheter. Of these one required catheterization after administration of an extradural narcotic.

DISCUSSION

When comparing two or more drugs it is important to make the comparisons between demonstrably equipotent doses. The best way to accomplish this is to establish and compare dose–response curves. This is not practical in a study such as this and it is possible to argue that the comparisons may be inaccurate as the "equipotent" doses were chosen arbitrarily. However, the similarity of the effect of the four drugs on breathing suggests that the doses were chosen with reasonable accuracy.

All four drugs in the doses used gave good relief of pain after operation. The fact that each of the four drugs was preferred by some of the patients demonstrates that all can be clinically useful and effective. Morphine was preferred by more patients than any other drug, although this preference failed to reach statistical significance. The duration of action of morphine and methadone are in good agreement with previously reported figures (Bromage, Camporesi and Chestnut, 1980). Pethidine and fentanyl gave effective relief but of shorter duration. It is interesting to note that the durations of action of the four drugs do not accord with the relative values of either their elimination half-lives

(Bochner et al., 1978; McClain and Hug, 1979), oil/water partition coefficients or distribution coefficients (Kaufman, Semo and Koski, 1975).

The plasma kinetics of morphine do not differ greatly after extradural administration from the kinetics following i.m. injection, with an elimination half-life of about 2 h (Weddel and Ritter, 1980). The plasma half-life of methadone after a single i.m. dose is 52 h (Verebely et al., 1975), therefore it is possible that, if extradural doses are administered repeatedly, say at 8-h intervals, significant systemic cumulation may occur.

Side-effects

All drugs caused a slight reduction in respiratory frequency, although none of the patients exhibited clinical respiratory depression. Severe, delayed respiratory depression has been reported after both extradural and intrathecal opiate administration, but was not encountered in our patients (Boas, 1980; Scott and McClure, 1979).

The heart rate was not significantly affected. As we found in a larger series, arterial systolic pressure was reduced slightly by morphine (Torda and Pybus, 1981). Pethidine was followed by significant reductions in both systolic and diastolic pressure. It needs to be emphasized that in no patient did the change cause concern.

Twelve of the patients arrived in the intensive care unit without urinary catheters. Although others have reported a high occurrence rate (Weddel and Ritter, 1980), only one of our patients—who had undergone pyelolithotomy—required catheterization for urinary retention. This frequency of retention accords well with our clinical impression that retention is more common in patients who receive lumbar or low thoracic extradural blocks than in those who receive high thoracic extradural narcotics.

Pruritus has now been widely reported (Torda et al., 1980; Bromage, Camporesi and Chestnut, 1980). Although it has been suggested that it is caused by the preservative in the morphine, this is probably not the case. The preservative, sodium metabisulphite, has been extensively used in adrenaline-containing solutions of lignocaine, yet itching is not a recognized side-effect. Itching has also been reported after the use of preservative-free morphine (Weddel and Ritter, 1980) and we have now encountered it after the use of pethidine. Whatever the mechanism, it does appear to occur most commonly after the administration of morphine.

Two of 24 patients suffered from nausea and vomiting. It is a low frequency when compared with its occurrence after i.m. opiates given for pain relief after operation. Although the sample in this study is small, the finding is in accord with other published studies (Magora et al., 1980).

This study demonstrates that any of the four drugs tested can be used effectively for extradural analgesia. There was no overwhelming advantage of one drug over the other except for the longer duration of action of morphine. Against this must be set the problem of pruritus. The effect of morphine on arterial systolic pressure does not appear to be of clinical significance. Whether the hypotensive effects of extradural pethidine are of clinical importance remains to be determined.

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COMPARAISON DE QUATRE ANALGESIQUES MORPHINOMIMETIQUES POUR L'ANALGESIE PERIDURALE

RESUME

On a comparé l'efficacité d'injections péridurales de sulfate de morphine 6 mg, méthadone 6 mg, péthidine 60 mg et fentanyl 60 μg pour soulager la douleur post-opératoire chez 24 patients. La durée moyenne de l'analgésie après injection de morphine a été de 12,3 h. Elle a été de 8,7 h pour la méthadone, de 6,6 h pour la péthidine et de 5,7 h pour le fentanyl. Il n'y a pas eu de différence significative d'efficacité entre les quatres agents. Il n'y a pas eu d'effets secondaires cliniquement importants sur la fréquence cardiaque, la fréquence respiratoire ou la pression artérielle, mais la pression artérielle systolique a diminué aprés morphine .et après péthidine. La péthidine entraîne également une baisse statistiquement significative de la pression artérielle diastolique.

VERGLEICH VON VIER NARKOTIKA BEI EPIDURALANALGESIE

ZUSAMMENFASSUNG

Die Wirkung von Epiduralinjektionen mit Morphinsulfat 6 mg, Methadon 6 mg, Pethidin 60 mg und Fentanyl 60 µg zur Schmerzbekämpfung nach Operationen wurde bei 24 Patienten verglichen. Die Durchschnittsdauer der Schmerzabnahme nach Gabe von Morphin betrug 12,3 Stunden, nach Methadon 8,7 Stunden, nach Pethidin 6,6 Stunden und nach Fentanyl 5,7 Stunden. Es ergaben sich keine signifikanten Unterschiede in der Wirksamkeit der vier Substanzen. Es gab keine Zeichen von klinischer Bedeutung bezüglich der Herzfrequenz, Atemfrequenz oder arteriellem Druck; der arterielle systolische Druck fiel jedoch ab nach Morphin und Pethidin. Pethidin verursachte auch einen statistisch signifikanten Abfall des diastolischen Druckes.

COMPARACION DE CUATRO NARCOTICOS UTILIZADOS PARA ANALGESIA EXTRADURAL

SUMARIO

Se comparó en 24 pacientes la efectividad de inyecciones extradurales de 6 mg de sulfato de morfina, de 6 mg de metadona, de 60 mg de petidina y de 60 μg de fentanilo, en lo tocante al alivio del dolor después de la operación. La duración media del alivio del dolor fue de 12,3 h para la morfina, 8,7 h para la metadona, 6,6 h para la petidina y 5,7 h para el fentanilo, después de administrar las respectivas inyecciones. No hubo una diferencia significativa en la eficacia de las cuatro drogas. No hubo efectos de importancia clínica en lo tocante al ritmo cardiaco, a la frecuencia respiratoria o a la presión arterial, pero hubo una disminución de la presión sistólica arterial después de administra morfina y petidina. La petidina también motivó una reducción estadisticamente significativa de la presión diastólica.

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I.V. GLYCERYL TRINITRATE: HAEMODYNAMIC EFFECTS AND CLINICAL USE IN CARDIAC SURGERY

R. BALE, A. POWLES AND R. WYATT

SUMMARY

A commercial preparation of glyceryl trinitrate for i.v. administration was assessed under both experimental and clinical conditions. The overall haemodynamic effects were beneficial during coronary artery grafting and aortic valve replacement, when the drug was given at a rate of $0.8\,\mu g\,kg^{-1}\,min^{-1}$ at which dose there was no appreciable effect on resistance vessels. No adverse side-effects occurred. There was no change in the activity of the preparation, whether diluted or not, over a 6-h period.

Hypertension unresponsive to analgesia or sedation may occur during heart surgery, particularly coronary artery by-pass grafting (CABG) and replacement of severely stenosed aortic valves (AVR). This increases left ventricular work, compromises suture lines and may be indicative of myocardial ischaemia as demonstrated by a decreased endocardial viability ratio (EVR) (Olinger et al., 1975; Kaplan, Dunbar and Jones, 1976):

$$\mathrm{EVR} = \frac{(\text{mean DAP} - \text{LVEDP}) \times \text{diastolic time}}{\text{mean SAP} \times \text{systolic time}}$$

where LVEDP = left ventricular end diastolic pressure; DAP = diastolic arterial pressure; SAP = systolic arterial pressure. It has become accepted as a useful indicator of subendocardial perfusion (which takes place exclusively in diastole) and carries a prognostic value (Hoffman and Buckberg, 1975, 1978). EVR less than 0.5 indicates that diffuse subendocardial necrosis will occur unless measures are taken to improve the myocardial oxygen supply : demand ratio, for example by intraaortic balloon pumping.

Many of the drugs used to control hypertension have serious disadvantages. Long acting vasodilators may result in unwanted hypotension at a later stage, phenothiazines and butyrophenones have sedative effects and compound respiratory depression from narcotics. Sodium nitroprusside (SNP) may cause cyanide intoxication if used over a prolonged period and has been reported by Armstrong and others (1975) to produce an adverse effect on EVR by reducing diastolic pressure and increasing intracoronary steal by its arteriolar dilator action.

A crushed glyceryl trinitrate (GTN) tablet in the buccolabial groove of such patients will transiently control such hypertension. The effect, however, is variable and not easy to adjust. Until very recently no preparation of i.v. GTN has been available and with additional controls imposed upon hospital pharmacies an *ad hoc* local preparation has not been feasible, so there is no available published work on the drug in the context of current U.K. practice.

A study was undertaken under experimental and clinical conditions to evaluate some of the haemodynamic effects of GTN during AVR and CABG. Permission was obtained from the Leicestershire Area Ethics Committee.

METHODS

The drug was supplied by Arnar–Stone Laboratories as a sterile, non-pyrogenic solution in 10-ml glass ampoules. The solution has the following composition: nitroglycerin* $0.5\,mg\,ml^{-1}$; lactose, US* $4.5\,mg\,ml^{-1}$; alcohol, USP $0.1\,ml\,ml^{-1}$ (10% v/v); monobasic potassium phosphate, USP $13.6\,mg\,ml^{-1}$ ($0.1\,mmol\,ml^{-1}$). (*From nitroglycerin 10% (w/w) in lactose USP.)

Experimental study

Ten patients were studied in detail while in a steady state at the conclusion of surgery (AVR, three patients; CABG, seven). After a control

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period GTN was infused i.v. at a constant rate of 0.8 $\mu g\,kg^{-1}\,min^{-1}$ until a further steady state was obtained, whereupon further measurements were made. The infusion was then discontinued, and observation continued until there was a return to control values. GTN was administered by placing the contents of one 5-mg ampoule into a Travenol 100-ml burette diluted with 5% dextrose 90 ml. A Sorenson "Dial-a-flow" was used to control the rate of infusion.

Clinical use

We have used i.v. GTN over a 6-month period for the following:

(1) In at least 10 patients for the treatment of acute perioperative hypertension in the presence of adequate analgesia (morphine 3–4.5 $mg\,kg^{-1}$) and normocarbia. Hypertension was defined as an arterial systolic pressure greater than 160 mm Hg or a diastolic pressure greater than 100 mm Hg, or both. In four of these patients the drug was administered as an infusion of GTN concentrate given from a 50-ml syringe gun over a period of 6 h. In the remainder of the patients the mode of administration was as described for the experimental study.

(2) To induce hypotension in cases of surgical difficulty: (a) slipping of the aortic side clamp (three patients); (b) to assist haemostasis under difficult conditions (two patients).

(3) To obtain sufficient haemodynamic improvement as to render aortic balloon counterpulsation unnecessary as judged by measuring EVR. The anaesthetic technique was the same in all patients (morphine, hyoscine and pancuronium, IPPV with a 50% oxygen in air mixture as described by May, Machin and Wyatt (1978)). Pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output were measured using a thermodilution Swan–Ganz catheter. Statistical analysis was performed using a paired Student's *t* test.

RESULTS

Experimental study (table I)

I.v. GTN in a constant dose of 0.8 $\mu g\,kg^{-1}\,min^{-1}$ produced a decrease in arterial systolic pressure not associated with an increase in heart rate or a decrease in diastolic pressure. No change in perfusion pressure could be demonstrated when GTN was administered with artificially generated pulsatile flow using a Stockert pump with the aorta cross-clamped and a venous pressure of zero, that is there appeared to be no effect on the resistance side of the circulation in the dose used. This is contrary to results published in the U.S.A. by Hempleman and others (1977).

There was a moderate but significant decrease in cardiac index (of the order of 10%) and, as a consequence, no significant changes in systemic or pulmonary vascular resistance were shown. The use of low doses of dopamine (3–5 $\mu g\,kg^{-1}\,min^{-1}$) to restore the cardiac output did not abolish the beneficial effects of GTN. Myocardial supply : demand ratio as measured by EVR was significantly improved. In all patients onset of action appeared complete within 4 min and in no patient was any haemodynamic effect discernible 5 min after discontinuing the GTN.

Clinical use

In four patients (CABG), two of whom were studied in the experimental series, an infusion of GTN concentrate was given for 6 h at a rate of 0.8 $\mu g\,kg^{-1}\,min^{-1}$. This proved effective in maintaining normotension with no instability of arterial pressure.

When bolus doses of GTN were used in an attempt to control brief periods of hypertension, doses of 50–100 μg were effective. With this method of administration a visible haemodynamic effect was seen within 1–2 min. This was followed by a continuous infusion. In three patients surgical difficulty because of slipping of the aortic side clamp was alleviated by the "bolus" technique and in two cases the induction of hypotension by GTN in previously normotensive individuals has, in conjunction with other measures, assisted in securing haemostasis under difficult conditions. In two instances sufficient haemodynamic improvement was obtained to render balloon counterpulsation unnecessary as judged by EVR. In one patient an improvement in cardiac output was observed after correction of a hypertensive state in the initial stages of a CABG surgery.

No adverse effects were observed. In particular, cerebral function as monitored with a Devices Cerebral Function Monitor was never compromised, no e.c.g. changes were seen, and there were no significant reductions in oxygen saturation or increase in shunt fraction. No methaemoglobin was detected on spectroscopic examina-

TABLE I. *Haemodynamic values and statistical analysis of patients in the experimental study. SA = surface area; AP = systemic arterial pressure; HR = heart rate;* $\overline{PAP}$ *= mean pulmonary artery pressure; RAP = right atrial pressure; PCW = pulmonary capillary wedge pressure; CO = cardiac output; CI = cardiac index; EVR = endocardial viability ratio; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index; B = before GTN administration; D = during GTN administration; SD = standard deviation;* P *= probability; n.s. = not statistically significant*

	SA	AP (mm Hg)		HR (beat min^{-1})		$\overline{PAP}$ (mm Hg)		RAP (mm Hg)		PCW (mm Hg)	
Patient	(m^2)	B	D	B	D	B	D	B	D	B	D
1	1.90	150/75	125/72	90	90	22	16	11	8	22	14
				(paced)							
2	1.90	121/78	96/68	90	90	26	16	12	9	22	12
3	1.40	100/44	80/42	90	92	22	16	18	16	23	15
4	1.40	110/60	90/60	80	85	17	8	15	12	15	5–12
5	1.85	160/60	130/60	105	100	17	15	15	10	15	10
6	2.15	155/85	140/85	105	105	25	18	8	8	15	12
7	1.95	140/80	125/80	89	82	16	12	10	8	12	9
8	1.90	138/68	130/70	74	78	26	23	14	12	22	20
9	2.05	140/75	124/72	120	126	29	23	16	15	20	16
10	1.80	122/80	110/80	88	90	28	15	12	9	15	11
Mean	Syst.	133.6	115.0	93.1	93.8	22.5	16.3	13.1	10.7	18.0	12.4
	Diast.	70.5	68.9								
SD	Syst.	19.85		13.54		4.46		2.99		4.10	
	Diast.	1.13									
P	Syst.	0.01		n.s.		0.01		0.05		0.02	
	Diast.	n.s.									

	SA	CO (litre min^{-1})		CI (litre min^{-1})		EVR		PVRI		SVRI	
Patient	(m^2)	B	D	B	D	B	D	B	D	B	D
1	1.90	4.66	4.37	2.45	2.30	0.90	1.16	0.13	0.86	36.28	35.20
2	1.90	4.80	4.31	2.42	2.27	0.90	1.21	1.78	1.62	33.18	36.00
3	1.40	4.91	4.20	3.50	3.00	0.67	0.77	0.20	0.44	12.73	12.88
4	1.40	3.67	3.06	2.62	2.18	0.79	1.14	0.60	1.50	23.52	26.53
5	1.85	7.98	6.08	4.31	3.29	0.48	0.69	0.46	1.52	22.79	22.31
6	2.15	5.73	5.38	2.66	2.50	0.40	0.57	3.87	2.39	37.64	38.09
7	1.95	6.45	5.65	3.30	2.89	0.86	1.10	1.31	1.26	27.20	30.02
8	1.90	4.75	4.20	2.50	2.21	0.82	0.93	1.73	1.50	30.03	35.28
9	2.05	6.07	5.00	2.96	2.44	0.59	0.68	3.15	3.00	27.24	30.41
10	1.80	4.60	4.29	2.50	2.38	0.65	0.75	4.04	1.53	32.08	33.98
Mean		5.34	4.65	2.92	2.54	0.70	0.89	1.73	1.56	28.36	30.11
SD		1.05		0.49		0.20		1.04		7.57	
P		<0.1	>0.05	0.05		0.02		n.s.		n.s.	

tion. User skin contamination did not produce headache or any other symptoms. No decline of activity of GTN was observed after 30 min in the diluted form or up to 6 h when undiluted.

DISCUSSION

The primary pharmacological action of GTN is relaxation of vascular smooth muscle (Goodman and Gilman, 1975), the effect being more marked on the capacitance side of the circulation. This promotes peripheral pooling of blood and decreases venous return, producing in turn a decrease in left ventricular pressure, myocardial wall tension, heart size and, ultimately, myocardial oxygen demand. As a result of the reduction in LVEDP subendocardial perfusion is increased (Winbury, Howe and Hefner, 1969;

Becker, Fortuin and Pitt, 1971; Mathes and Rival, 1971; Chiarello et al., 1976). A more favourable myocardial oxygen supply : demand ratio is thus achieved.

In the past few years the popularity of CABG operations has increased and has been accompanied by a high frequency (5–40%) of perioperative myocardial infarction (Mundth and Austen, 1975). It is important that steps are taken to treat the factors which decrease the myocardial supply : demand ratio. (1) increased myocardial wall tension, secondary to either hypertension (increased afterload) or increased filling pressure (increased preload), (2) increased contractility and (3) increased heart rate (Awan et al., 1976).

Sublingual GTN has been used for more than a century in the treatment of angina pectoris. Viljoen (1968) used i.m. GTN during internal mammary implantation surgery. Many studies have been undertaken in recent years on both i.v. and i.m. administration of GTN in the U.S.A. In these American studies GTN has been shown to reduce preload and afterload and improve blood flow to ischaemic areas of myocardium, whilst SNP reduces the flow (Chiarello et al., 1976). It is effective in relieving coronary artery spasm in patients suffering from Prinzmetal's variant angina pectoris, probably by a direct dilator effect on the coronary arteries (Oliva, Potts and Pluss, 1973; Krantz, Viljoen and Gilbert, 1980). GTN has also been shown to redistribute blood to the subendocardium (Becker, Fortuin and Pitt, 1971; Mathes and Rival, 1971; Chiarello et al., 1976). A reduction in pulmonary vascular resistance has been demonstrated by Hempleman and others (1977).

In this study GTN caused a reduction of preload and arterial systolic pressure without change in diastolic pressure or heart rate, thus improving EVR. A decrease in cardiac output, readily reversed by low-dose dopamine, was seen. Unlike the American experience, no demonstrable effect on systemic or pulmonary vascular resistance was observed, neither did we see any significant increase in shunt fraction. These differences may be partly explained by dissimilar anaesthetic technique; we used no inhalation anaesthetic agents such as halothane or nitrous oxide which have a negative inotropic effect and potentiate GTN. The absence of an increase in shunt fraction may be attributable to the regional hypoxic vasoconstrictor mechanism which regulates $\dot{V}/\dot{Q}$ balance, is abolished by nitrous oxide, but preserved with morphine. The absence of any effect on pulmonary vascular resistance is disappointing, but separate studies should be performed to determine if the drug affects abnormally increased resistance such as occurs in mitral valve disease.

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EFFETS HEMODYNAMIQUES ET USAGE CLINIQUE DU TRINITRATE DE GLYCERYLE POUR LES INTERVENTIONS CHIRURGICALES AU COEUR

RESUME

Une préparation commerciale de trinitrate de glycéryle pour administration par voie intraveineuse a été évaluée dans des conditions expérimentales et dans des conditions cliniques. Les effets hémodynamiques ont dans l'ensemble été bénéfiques lors d'une greffe de l'artère coronaire et du remplacement d'une valvule aortique, alors que ce médicament était administré à raison de 0,8 μg kg^{-1} min^{-1}, dose qui n'a pratiquement pas affecté les vaisseaux de résistance. Il ne s'est produit aucun effet secondaire adverse. Il n'y a eu aucun changement dans l'activité de la préparation, diluée ou non, au cours d'une période de 6 h.

INTRAVENÖS VERABREICHTES GLYZERYLTRINITRAT: HÄMODYNAMISCHE WIRKUNGEN UND KLINISCHE VERWENDUNG BEI HERZCHIRURGIE

ZUSAMMENFASSUNG

Ein Handelspräparat von Glyzeryltrinitrat zur intravenösen Verabreichung wurde unter experimentellen und unter klinischen Bedingungen untersucht. Die allgemeinen hämodynamischen Wirkungen während Koronararterienverpflanzung und Aortenklappeneinsatz waren günstig, wenn die Droge mit 0,8 μg kg^{-1} min^{-1} verabreicht wurde, bei welcher Dosis sich keine erkennbaren Auswirkungen auf den Gefässwiderstand zeigten. Es kam zu keinen schädlichen Nebenwirkungen. Die Wirkung des Präparates, ob verdünnt oder nicht, veränderte sich über eine Periode von 6 Stunden nicht.

TRINITRATO DE GLICERILO INTRAVENOSO: EFECTOS HEMODINAMICOS Y USO CLINICO EN LAS OPERACIONES DE CORAZON

SUMARIO

Se evaluó una preparación comercial de trinitrato de glicerilo a usar en administraciones intravenosas, tanto bajo condiciones experimentales como clínicas. Los efectos hemodinámicos globales fueron beneficiosos durante el injerto de la arteria coronaria y durante la sustitución de la válvula aórtica, cuando la droga se administró a un régimen de 0,8 μg kg^{-1} min^{-1}, dosis a la que no se detectaron efectos apreciables en la resistencia de los vasos. No se presentaron efectos adversos. No hubo cambio alguno en la actividad de la preparación por espacio de 6 h, independientemente de que dicha preparación fuera diluida o no.

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EFFECT OF PREANAESTHETIC MEDICATION ON ANAESTHESIA WITH ICI 35868

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SUMMARY

The effect of three commonly used premedicants and a control on anaesthesia with ICI 35868 is described. Two randomized studies were performed—one a group study of induction characteristics at 2 mg kg^{-1} and the other a detailed study in patients undergoing minor gynaecological surgery with an induction dose of 1.5 mg kg^{-1} and maintenance with incremental doses plus 66% nitrous oxide in oxygen. Premedication had little effect on the already good induction characteristics. Only heavy opiate premedication produced reliable induction at 1.5 mg kg^{-1}, but with an increase in side-effects. Diazepam appears to be the premedicant of choice, although the overall frequency of pain on injection has not been affected by premedication.

ICI 35868 (di-isopropyl phenol) is an i.v. anaesthetic agent, the clinical use of which was first described by Kay and Rolly in 1977. Animal studies had shown that it was similar to methohexitone in potency and toxicity, with little evidence of cumulation from repeated doses. Like thiopentone, effective doses cause sleep in one arm–brain circulation time (Briggs et al., 1981). It has recently been compared with Althesin (Kay and Stephenson, 1980) and with methohexitone (Rutter et al., 1980). Several clinical reports suggest that it is a drug with many promising features (Rutter et al., 1980; Major et al., 1981) and well worthy of further study.

In the early studies, Kay and Rolly (1977) found 1.0 mg kg^{-1} to be a satisfactory induction dose in unpremedicated patients. This is at variance with our own experience with the drug. In a dose-finding study, Briggs and colleagues (1981) found the minimum "sleep" dose to be 1.75 mg kg^{-1}, injected over 20 s. We recommended 2.0 mg kg^{-1} as the most satisfactory dose for routine clinical use, although Major and colleagues (1981) have since reported one failed induction out of 10 when this dose was given over 30 s. There have been no detailed studies on the influence of premedication on its clinical action and potency.

This paper reports an evaluation of the induction characteristics following our recommended dose of 2.0 mg kg^{-1} in patients given one of three commonly used premedicants and also the effect of these premedicants on a lower dose (1.5 mg kg^{-1}). This last was a well controlled randomized study involving only two anaesthetists in which ICI 35868 was used as the main agent for a standard operation (detailed study), while the first studies involved a number of administrators who limited their observations to the immediate peri-induction period (group study).

METHODS

The patients in both studies were all fit adults aged 18–65 yr. They had no history of atopy or allergy nor had they received a Cremophor-containing anaesthetic in the previous 6 months. Informed consent was obtained from all patients. The induction doses were injected over a period of 20 s; the site of injection was noted and patients were asked if the injection was painful.

Premedicants. The four premedicant groups were: diazepam 10 mg given orally; pethidine 50–75 mg with atropine 0.6 mg i.m.; papaveretum 10–20 mg with hyoscine 0.2–0.4 mg i.m.; nil.

Detailed study. The patients were all undergoing minor gynaecological operations and anaesthesia was induced and maintained with ICI 35868, with 66% nitrous oxide in oxygen, the

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initial dose being 1.5 mg kg^{-1} followed by incremental doses of 10 mg as required to control reactive movements. The presence of excitatory effects (involuntary movements, tremor or hypertonus), respiratory upset (cough or hiccup) or respiratory depression (apnoea lasting for longer than 15 s) was noted. Arterial pressure was measured by auscultation before induction and at 1-min intervals throughout anaesthesia. The observations made during anaesthesia were standardized as in reported studies from this department (Dundee and Moore, 1961; Clarke et al., 1972; Zacharias et al., 1979). Patients were all followed up for 6 h and any untoward sequelae noted.

The patients were allocated at random to one of the four premedicant groups and active premedicants were given 60–90 min before operation. There were 20 patients in each of the active premedicant groups and 40 who received no premedication.

Group study. In patients of both sexes, undergoing a variety of operations anaesthesia was induced with ICI 35 868 2.0 mg kg^{-1}. Observations were as described above and the recordings were limited to a period of 2 min following induction, after which anaesthesia was continued with a variety of techniques. A total of eight anaesthetists took part in the study in which allocation to the various premedicant groups was again at random.

RESULTS

Detailed study. The patients in the four groups were broadly comparable with respect to average age, weight and duration of anaesthesia.

Only papaveretum with hyoscine premedication made 1.5 mg kg^{-1} a reliable induction dose (table I). The average total dose of ICI 35 868 was less in those patients given diazepam ($t = 2.85$; $P < 0.01$) and papaveretum with hyoscine ($t = 5.96$; $P < 0.001$) premedication than in the control group.

On the debit side, papaveretum with hyoscine premedication was associated with a greater frequency of marked respiratory depression than control ($\chi^2 = 43.8$; $P < 0.001$), although it did not affect the frequency of notable reductions in arterial systolic pressure. It was also associated with a smaller number of patients who had control of their protective reflexes 2 min after discontinuing the nitrous oxide, although the difference from the other series was not statistically significant.

Group study. This was carried out in four sets, each of 50 patients, which were broadly comparable with respect to average age and weight (table II). Even the 2.0 mg kg^{-1} dose was not adequate

TABLE I. *Details of patients given induction doses of 1.5 mg kg^{-1} ICI 35 868 (mean ± SEM) and details of anaesthetic and postanaesthetic sequelae*

	Premedication			
	Nil	Diazepam	Pethidine–atropine	Papaveretum–hyoscine
No.	40	20	20	20
Age (yr)	35 ± 1.9	40 ± 2.2	34 ± 2.4	35 ± 2.4
Weight (kg)	60 ± 1.9	64 ± 2.2	62 ± 3.8	60 ± 1.6
Duration of anaesthesia (min)	9.5 ± 0.5	7.8 ± 0.5	9.6 ± 1.3	9.6 ± 0.7
Total dose (mg kg^{-1})	3.0 ± 0.12	2.5 ± 0.13	3.2 ± 0.24	2.0 ± 0.09
Anaesthesia induced	35	19	17	20
Marked respiratory depression	2	3	0	6
Decrease in systolic AP > 20 mm Hg	5	4	2	3
After operation				
"Safe" 2 min after nitrous oxide off	34	19	17	15
Nausea or vomiting, or both (0–6 h)	3	0	1	2

TABLE II. *Details of patients given induction doses of ICI 35 868 2 mg kg^{-1} in group study (mean ± SEM) and details of anaesthetic sequelae. There were 50 patients in each series*

	Premedication			
	Nil	Diazepam	Pethidine–atropine	Papaveretum–hyoscine
Age (yr)	37 ± 1.9	37 ± 2.3	39 ± 2.1	38 ± 2.2
Weight (kg)	60 ± 1.6	60 ± 1.5	61 ± 1.3	61 ± 1.6
Anaesthesia induced	45	50	49	49
Marked respiratory depression	1	0	13	11
Decrease in systolic pressure > 20 mm Hg	10	11	12	23

TABLE III. *Frequency of pain on injection related to injection site (pooled data from both studies)*

	Premedication			
Site of injection	Nil	Diazepam	Pethidine–atropine	Papaveretum–hyoscine
Antecubital fossa				
Total number	21	22	33	26
Pain	3	0	2	2
Hand or wrist				
Total number	20	11	17	26
Pain	6	3	7	11

to ensure a consistent induction of anaesthesia in unpremedicated patients. Any form of opiate premedication increased the frequency of marked respiratory depression to a significant extent ($P < 0.01$), while premedication with papaveretum and hyoscine was associated with more frequent hypotension than in the other two groups ($P < 0.001$).

The overall frequency of reductions in arterial systolic pressure in excess of 20 mm Hg was 28% in patients induced with 2 mg kg^{-1} compared with 14% of those given 1.5 mg kg^{-1}, but this difference was not statistically significant.

The pooled data from the two studies relating the frequency of injection site pain to the site of injection (table III) shows a highly significant difference ($P < 0.001$) between the frequency with antecubital fossae injections (9%) and those given in the hand or wrist (31%).

DISCUSSION

Compared with drugs such as methohexitone, minaxolone and etomidate, ICI 35 868 can be classed as a good induction agent with minimal involuntary movement following normal doses. There is thus little room for improvement with premedication, nor is it an essential part of the anaesthetic technique. In fact papaveretum with hyoscine premedication introduces undesirable side-effects, although it does make the smaller dose (1.5 mg kg^{-1}) acceptable for induction. Of those agents studied diazepam would appear to be the premedication of choice with ICI 35 868.

It is unfortunate that analgesic premedication does not influence the pain experienced when ICI 35 868 is injected into small veins of the hand and wrist. The overall frequency of pain in this study was identical with that reported by Briggs and others (1981) and, when the two series were combined, giving the frequency of pain as 5% with antecubital injections and 37% with hand or wrist injections, the need for an alternative pain-free formulation became more obvious.

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EFFETS DE LA PREMEDICATION SUR L'ANESTHESIE AU ICI 35 868

RESUME

On décrit les effets de trois agents couramment utilisés en prémédication et d'un témoin sur l'anesthésie à l'ICI 35 868. Deux études randomisées ont été faites, une étude de groupe des caractéristiques d'induction à 2 mg kg^{-1}, et une étude détaillée chez des sujets subissant des actes de chirurgie gynécologique mineure avec une dose d'induction de 1,5 mg kg^{-1} et un entretien par des doses croissantes associées à 66% de protoxyde d'azote dans l'oxygène. La prémédication a peu d'effet sur les caractéristiques d'induction déjà bonnes. Seule une prémédication morphinomimétique lourde permet une induction fiable à 1,5 mg kg^{-1} mais au prix d'une augmentation des effets secondaires. Le diazepam apparait comme l'agent de prémédication de choix bien que la fréquence globale de douleur à l'injection n'ait pas été modifiée par la prémedication.

DIE WIRKUNG EINER PRÄMEDIKATION AUF DIE ANÄSTHESIE MIT ICI 35 868

ZUSAMMENFASSUNG

Die Wirkung von drei allgemein gebräuchlichen Medikamenten in Zusammenhang mit einer ICI 35 868 Anästhesie wird beschrieben. Zwei randomisierte Untersuchungen wurden durchgeführt. In der einen Gruppe wurde die Einleitung mit 2 mg kg^{-1}, in der anderen eine detaillierte Studie an Patienten, die sich einer kleinen gynäkologischen Operation unterzogen hatten, durchgeführt. Bei diesen wurde die Einleitungsdosierung auf 1,5 mg kg^{-1} festgesetzt und die Aufrechterhaltung mit zunehmender Dosierung in Kombination von 66% Stickoxydul in Sauerstoff erreicht. Die Prämedikation hatte geringe Wirkung auf die bereits guten Einleitungseigenschaften. Nur eine starke Prämedikation mit Opiaten zeigte eine verlässliche Induktion bei 1,5 mg kg^{-1}, jedoch nahmen die Nebenwirkungen zu. Diazepam scheint die Prämedikation der Wahl zu sein, obwohl die allgemeine Inzidenz des Injektionsschmerzes durch die Prämedikation nicht beeinflusst werden konnte.

EFECTO DE LA MEDICACION PREANESTETICA SOBRE LA ANESTESIA CON ICI 35 868

SUMARIO

Se describe el efecto de tres substancias de premedicación común y el control de la anestesia con ICI 35 868. Se llevaron a cabo dos estudios al azar—uno en un estudio de grupo de características de inducción con 2 mg kg^{-1}, y el otro un estudio detallado en pacientes sometidos a operaciones ginecológicas menores con una dosis de inducción de 1,5 mg kg^{-1}, y mantenimiento con dosis incrementadas además de un 66% óxido nitroso en oxígeno. La premedicación tuvo poco efecto sobre las características yá buenas de la inducción. Una premedicación fuerte con opiatos sólo produjo una inducción fiable con 1,5 mg kg^{-1}, pero con un aumento de los efectos secundarios. El diazepam parece ser la substancia de premedicación la más selecta, aunque la frecuencia general del dolor al momento de la inyección no fue afectada por la premedicación.

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COMPARISON OF THE EFFECT OF DIISOPROPYL PHENOL (ICI 35 868) AND THIOPENTONE ON RESPONSE TO SOMATIC PAIN

L. P. BRIGGS, J. W. DUNDEE, M. BAHAR AND R. S. J. CLARKE

SUMMARY

The response to somatic pain with sub-hypnotic doses of ICI 35 868 (diisopropyl phenol in cremophor) and thiopentone was compared using tibial pressure algesimetry. Studies were also carried out following recovery from larger doses of both drugs. The patients underwent minor gynaecological procedures using only one of the two i.v. agents and nitrous oxide in oxygen. The studies confirmed the known antanalgesic action of thiopentone and demonstrated that diisopropyl phenol has an analgesic action which is an attractive feature in an i.v. anaesthetic agent.

It is generally accepted that small doses of thiopentone cause an increased sensitivity to somatic pain (Clutton-Brock, 1960; Dundee and Moore, 1960a). This antanalgesic action adversely influences the use of thiopentone as sole anaesthetic. The ideal i.v. anaesthetic should either have a slight analgesic action or at least not increase sensitivity to pain (Dundee, 1979). For this reason, it is important that evaluation of potential new i.v. anaesthetics should include a study of their effect on somatic pain in man.

This paper reports algesimetry studies with small sub-hypnotic doses of the new i.v. anaesthetic, diisopropyl phenol (Kay and Stephenson, 1980; Rutter et al., 1980) and these are compared with similar studies using thiopentone. It also reports corresponding findings in the period after operation in patients who received large doses of each drug as principal anaesthetic.

The method used was tibial pressure algesimetry which was described by Clutton-Brock (1957) and evaluated by Dundee and Moore (1960a). It has been used widely in the study of i.v. anaesthetics including thiopentone (Dundee, 1960), propanidid (Dundee and Clarke, 1965), Althesin (Arora, Carson and Dundee, 1972) and ketamine (Bovill and Dundee, 1971) as well as some inhalation agents (Dundee and Moore, 1960b).

METHODS

The studies were carried out in fit unpremedicated women undergoing minor gynaecological operations. There was no choice as to which agent was used except that patients with a history of exposure to cremophor or with known allergy or atopy were not given diisopropyl phenol. The studies were carried out immediately before induction of anaesthesia, the procedure having been explained to the patients and their consent obtained.

Gradually increasing pressure was applied to the skin overlying the anterior surface of the middle third of the tibia using an inverted modified domestic balance with a metal disc of 9.2 mm diameter which had replaced the tray. Patients were asked to identify when the sense of pressure first changed to pain and when the pain became intolerable or they moved their legs in response to the pain. The first reading was taken as the pain "threshold" and the latter termed pain "response". The readings were measured as the gradations on the scales at which the various endpoints appeared. All observations in one patient were carried out by the same observer on one leg either in a quiet area adjoining the operating theatre or in the theatre itself before anaesthesia was induced. The average of the threshold and response readings was used for analysis of the data.

A minimum of two control readings were taken before any drug was injected and if these were within the accepted range of error of the method, the study commenced. Otherwise, a third reading was taken and if the scatter was still excessive, the

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patient was excluded from the study. Previous experience (Dundee and Moore, 1960a) has shown that duplicate readings should not vary by more than one unit on the scales. Patients who found the procedure to be distressing and who were unable to concentrate were also excluded.

The study was divided into two parts. In the first, the patient received sub-anaesthetic doses of either of the two drugs under study and algesimetry readings were taken at 1-min intervals for 3 min after injection. Twenty patients were studied with each of the drugs. With diisopropyl phenol, the initial study in 10 patients was with 0.25 mg kg^{-1} which was repeated after 3 min. A further 10 patients were given doses of 0.5 mg kg^{-1}. The doses of thiopentone given to the other 20 patients ranged from 0.4 to 1.4 mg kg^{-1}. When the study was completed, the patients were given a full induction dose of one or other of the agents and anaesthesia was carried out in the normal manner. They were not subjected to any further studies.

In the second study, control readings were taken as above, but anaesthesia was induced with normal doses of either diisopropyl phenol 2 mg kg^{-1} or thiopentone 4 mg kg^{-1}. Anaesthesia was maintained with intermittent doses of the induction agent and nitrous oxide in oxygen, but no other agents were given. Nitrous oxide was discontinued at the end of the operation and the algesimetry readings repeated as soon as the patients were sufficiently conscious to respond to commands. Repeat readings were carried out at intervals of 2–3 min depending on the results. This investigation was continued until the readings had returned to within the accepted range of variation from the preoperative control. Twenty patients were studied after the large doses of diisopropyl phenol, and 18 after thiopentone.

In presenting data for sub-hypnotic doses, the frequency is given of what are considered to be significant changes from control readings of either analgesia or antanalgesia. It is not considered that this is a sufficiently quantitative method to grade the response other than being indicative of analgesia or antanalgesia (increase or decrease in readings from control). Only a statistical comparison of the frequency of these changes using the χ^2 analysis has been made.

In the period after operation, the variation from the preoperative control readings of individual patients is shown and results illustrated with typical cases. The results were such that a statistical evaluation was not necessary.

RESULTS

Results from patients who received sub-hypnotic doses of the drugs are given in table I, while table II illustrates the results in the 10 patients who were given a second dose of diisopropyl phenol 0.25 mg kg^{-1}. There is a significant difference ($\chi^2 = 14.08$; $P < 0.001$) between the responses of the patients to the two drugs. Most of those who received diisopropyl phenol showed either no change or analgesia, while antanalgesia was a feature of patient receiving thiopentone.

TABLE I. *Frequency of changes in algesimetry readings 1 min after injection of sub-hypnotic doses of diisopropyl phenol and thiopentone*

	Diisopropyl phenol 0.25–0.5 mg kg^{-1}	Thiopentone 0.5–1.5 mg kg^{-1}
Analgesia	7	2
No effect	12	6
Antanalgesia	1	12

TABLE II. *Frequency of changes in algesimetry readings following two doses each of diisopropyl phenol 0.25 mg kg^{-1}*

	1st dose ↓ 0	1	2	3	2nd dose ↓	4	5 min
Increase		2	2	4		4	5
No change		7	7	5		5	4
Decrease		1	1	1		1	1

The postoperative findings in 20 patients who received an average of diisopropyl phenol 4.1 mg kg^{-1} with nitrous oxide in oxygen for minor operations is shown in figure 1. Timing was taken from the end of anaesthesia, all patients being awake within 5 min. The figure demonstrates a residual analgesic action persisting for 40–50 min in some patients. A similar study with thiopentone in 18 patients who received doses averaging 6.2 mg kg^{-1} (fig. 2) shows a mainly antanalgesic effect persisting for up to 300 min.

The difference between the two drugs is more obvious in figures 3 and 4 which show typical findings with each agent in six patients.

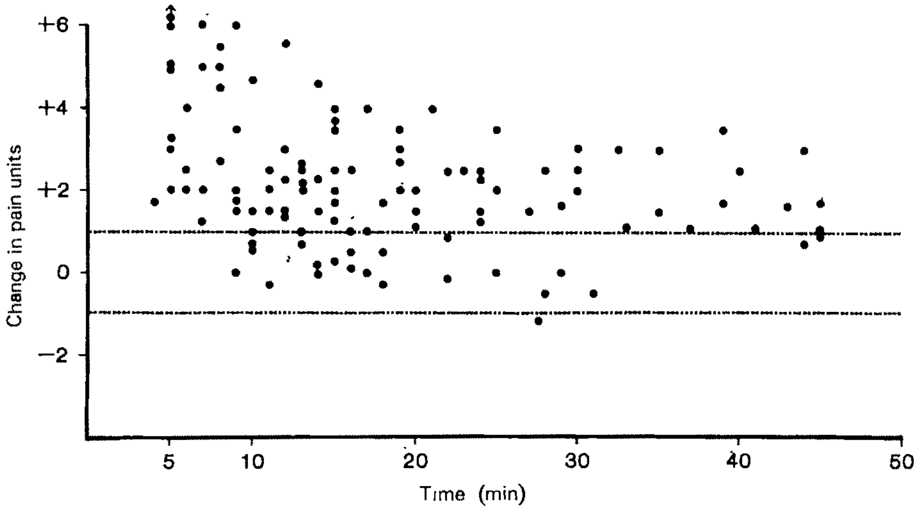

FIG. 1. Changes in postoperative pain readings following large doses of diisopropyl phenol compared with preoperative controls. ... = Range of expected normal variations in readings.

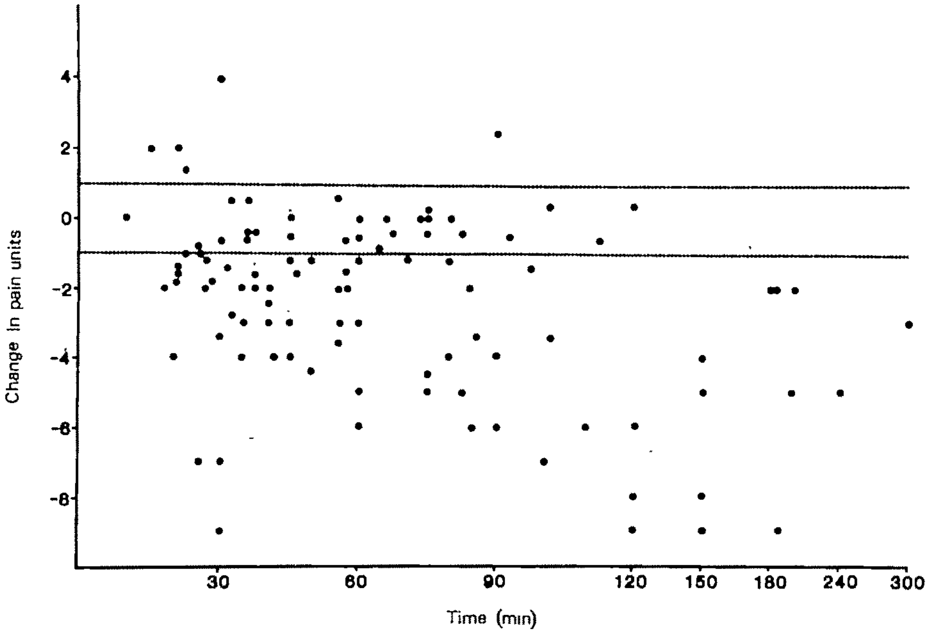

FIG. 2. Changes in postoperative pain readings following large doses of thiopentone compared with preoperative controls. ... = Range of expected normal variations in readings.

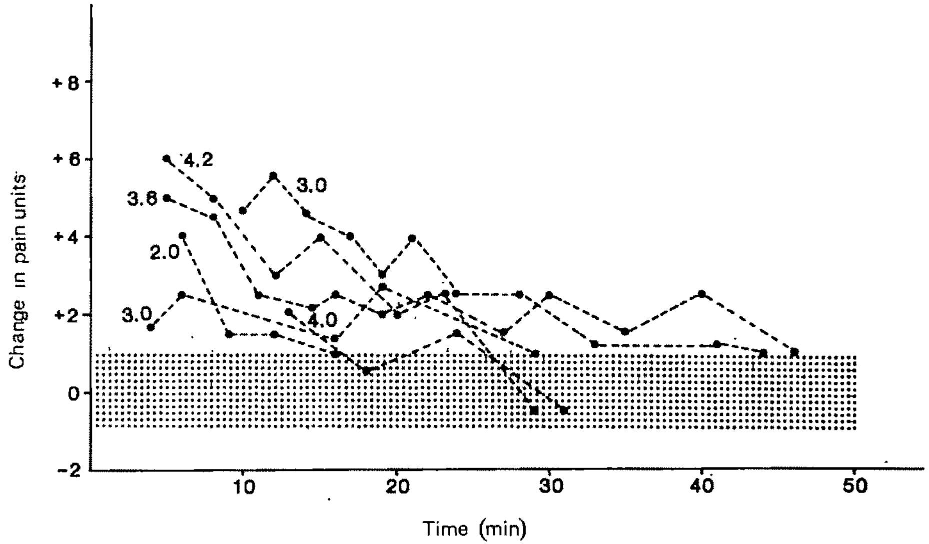

FIG. 3. Change in pain units in the postoperative period plotted in six typical patients who received diisopropyl phenol. Figures indicate dosage in mg kg^{-1}.

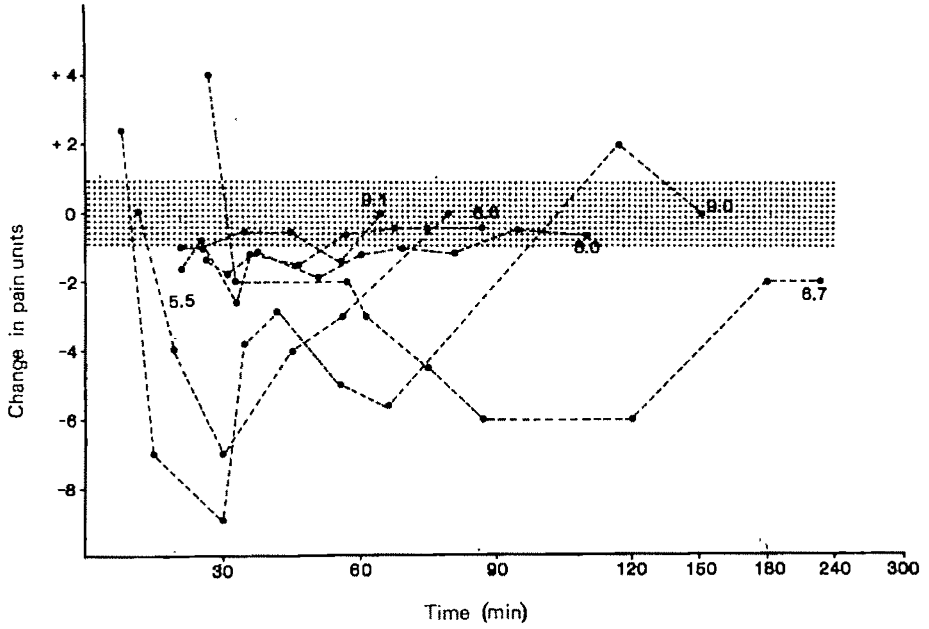

FIG. 4. Change in pain units in the postoperative period plotted in six typical patients who received thiopentone. Figures indicate dosage in mg kg^{-1}.

DISCUSSION

Results with thiopentone are quantitatively and qualitatively similar to those obtained some 20 years ago with the same method (Dundee, 1960) and demonstrate a state of antanalgesia or hyperaesthesia (Keats, 1965). However, this state of increased sensitivity to somatic pain was not a feature of either small sub-hypnotic doses of diisopropyl phenol or of recovery from large full anaesthetic doses. The two drugs behaved differently in both the preinduction and recovery periods and were opposite in their effect on patient appreciation of somatic pain.

There is no obvious explanation for the difference in response to the two drugs although there have been several attempts made to explain the antanalgesic action of thiopentone (Clutton-Brock, 1960; Brazier, 1961). A transient analgesic action has been demonstrated with propanidid (Dundee and Clarke, 1965), while ketamine is shown to have a more prolonged analgesic action. This latter effect has been attributed to an increase in circulating catecholamines. No comparable data are available for the drugs used in the present study.

These findings agree with the clinical action of the two drugs. Although experience with diisopropyl phenol is limited, patients have not been found to react vigorously to stimuli under light anaesthesia as commonly occurs with thiopentone. Undoubtedly, this would make it a more versatile drug for minor procedures in which it could be used as sole agent.

One might suggest cremophor as an agent in inducing analgesia as it is the solvent used for both propanidid and diisopropyl phenol. There have been no reports of its analgesic action and this is an unlikely explanation, as the solution of ketamine which has a definite analgesic effect is aqueous.

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COMPARAISON DE L'EFFET DU DIISOPROPYL PHENOL (ICI 35868) ET DU THIOPENTAL SUR LA REPONSE A LA DOULEUR SOMATIQUE

RESUME

On a comparé la réponse à la douleur somatique sous des doses infra-hypnotiques d'ICI 35868 (diisopropyl phénol dissous dans du cremophore) et de thiopental, en utilisant l'algésimétrie par pression tibiale. Des mesures ont également été faites après le réveil suivant une anesthésie avec des doses plus importantes des deux produits. Les patientes avaient subi des actes de chirurgie gynécologique mineure en n'utilisant que l'un des deux agents par voie intraveineuse et du protoxyde d'azote dans l'oxygène. Ces études ont confirmé l'action antianalgésique du thiopental et ont montré que le diisopropyl phénol a une action analgésique, ce qui est une propriété intéressante chez un anesthésique intraveineux.

VERGLEICH DER WIRKUNG VON DIISOPROPYLPHENOL UND THIOPENTONE AUF DIE SOMATISHCE SCHMERZREAKTION

ZUSAMMENFASSUNG

Die Antwort auf somatischen Schmerz mit subhypnotischen Dosen von ICI 35 868 (Diisopropylphenol in Cremophor) und Thiopentone wurde mit Hilfe der Tibial-Druck-Algesimetrie verglichen. Es wurden auch Untersuchungen durchgeführt, die sich auf die Erholungsphase nach Einnahme grösserer Dosen beider Substanzen erstreckten. Die Patienten unterzogen sich kleinerer gynäkologischer Operationen, bei denen sie lediglich eines der beiden i.v. Substanzen in Kombination mit stickoxydul und Sauerstoff erhielten. Die Studien bestätigten die bekannte antianalgetische Wirkung von Thiopenton und bewiesen, dass Diisopropylphenol eine analgetische Wirkung besitzt, was für ein i.v. Anästhetikum ein bemerkenswerter Aspekt ist.

COMPARACION DEL EFECTO DEL DIISOPROPIL FENOL (ICI 35868) Y DE LA TIOPENTONA SOBRE RESPUESTA AL DOLOR SOMATICO

SUMARIO

Se comparó la respuesta al dolor somático con dosis subhipnóticas de ICI 35868 (diisopropil fenol en cremofor) y la tiopentona, al usar la algesimetría de la presión tibial. También se llevaron a cabo estudios después de la recuperación de dosis mayores de ambas substancias. Las pacientes fueron sometidas a operaciones ginecológicas menores y se usó solamente uno de los dos agentes i.v. y óxido nitroso en oxígeno. Los estudios confirmaron la acción antanalgésica conocida de la tiopentona y demonstraron que el diisopropil fenol posee una acción analgésica que constituye un rasgo atrayente en un agente anestético i.v.

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EFFECTS OF POSTURE ON THE SPREAD OF SPINAL ANAESTHESIA WITH ISOBARIC 0.75% OR 0.5% BUPIVACAINE

M. TUOMINEN, E. KALSO AND P. H. ROSENBERG

SUMMARY

In a double-blind study the effects of posture on the the spread of 3 ml of isobaric bupivacaine 5 and 7.5 mg ml^{-1} were compared after intrathecal injection in 40 patients undergoing orthopaedic surgery. Three millilitre of isobaric bupivacaine 7.5 mg ml^{-1} administered with the patient in a sitting position during and for 2.5 min after injection produced the highest spread of analgesia (T4). Horizontal posture, and the smaller dose in both positions, resulted in spread of analgesia to T7–8. Motor block in the legs was good in all cases. Horizontal posture at the time of injection resulted in the longest mean duration of analgesia and motor block, although there was no statistically significant difference in mean times between the groups. The longest mean duration of pin-prick analgesia (329 ± 23 min) was in the patients injected in the horizontal posture with bupivacaine 7.5 mg ml^{-1}. The course of anaesthesia and recovery were uneventful in all patients.

Isobaric anaesthetic solutions seem to spread very little following intrathecal injection (Kitahara, Kuri and Yoshida, 1956), but an increase in volume has resulted in an increase in segmental spread of analgesia (Nolte and Stark, 1979). Tompkins and Neigh (1977) did not consider the volume of the anaesthetic solution essential for the spread of analgesia. However, there is agreement about the influence on spread of analgesia of some other factors, such as the density of the local anaesthetic solution, the interspace used for injection, the force and speed of injection, and the performance of barbotage (Lund, 1971).

Isobaric bupivacaine has been used successfully for spinal anaesthesia (Stratmann et al., 1979; Nightingale and Marstrand, 1981). We have found no reports of the influence of posture during injection of isobaric bupivacaine on spread and other characteristics of the block. We have now studied the effect of posture during injection of two different doses of isobaric bupivacaine for spinal anaesthesia.

PATIENTS AND METHODS

We studied 40 patients, undergoing orthopaedic surgery, who gave informed consent. There was no history of sensitivity to local anaesthetics. All patients were in good general health and were not taking drugs known to modify the action of local anaesthetics. Patient characteristics and the operations are shown in table I. Premedication comprised diazepam 5–15 mg orally 1.5–2 h and atropine 0.01 mg kg^{-1} about 1 h before anaesthesia.

Before the subarachnoid injection, Ringer solution 8 ml kg^{-1} was administered by rapid i.v. infusion; this was repeated over 20 min immediately after the injection. A mid-line lumbar puncture was performed through the L3–4 intervertebral space with a 25-gauge needle. The position of the needle was confirmed by barbotage (0.2–0.4 ml) before and after administration of the drug. The speed of injection was approximately 1 ml in 3 s.

The local anaesthetic was injected with the patients horizontal and on the side or sitting in random order. Three millilitre of the test drug was given in a double-blind fashion from a coded ampoule containing isobaric bupivacaine either 5 mg ml^{-1} or 7.5 mg ml^{-1} (Astra Läkemedel Ab, Sweden). Thus each patient received isobaric bupivacaine either 15 mg or 22.5 mg (1 g cm^{-3}) intrathecally, forming different groups for comparison: isobaric bupivacaine 5 mg ml^{-1} received in the sitting (group I) or horizontal (group II) position; in groups III and IV isobaric bupivacaine 7.5 mg ml^{-1} was administered with the patient in the sitting or horizontal position, respectively. Patients in the horizontal position (operation side upwards) were moved to the supine position immediately after administration

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of the drug, whereas the patients sitting during injection were left in the same position for 2.5 min and then moved to the horizontal supine position.

TABLE I. *Patient characteristics and type of surgery. Ranges in parentheses*

	Group I (0.5% sitting)	Group II (0.5% horizontal)	Group III (0.75% sitting)	Group IV (0.75% horizontal)
Sex (M/F)	4/6	2/8	2/8	3/7
Age (yr)	68 (63–75)	64 (53–74)	62 (54–74)	65 (47–70)
Weight (kg)	70 (55–84)	70 (63–78)	69 (50–90)	78 (60–96)
Height (cm)	164 (150–179)	162 (153–172)	163 (151–184)	166 (153–182)
Duration of operation (min ± SEM)	126 ± 10	98 ± 6	110 ± 9	106 ± 10
Type of surgery				
Arthroplasty of hip or knee	9	5	8	6
Other: hip		2		
knee	1	2	1	2
foot		1	1	
femur				2

TABLE II. *Characteristics of the spinal block in different groups. Values are means ± SEM, or number of patients*

	Max. spread of analgesia (segments)	Time of latency of max. spread (min)	No. of total motor blocks	Time of latency of total motor block (min)	Duration of analgesia (min)	Duration of motor block (min)	Time to first analgesic (min)
Group I (0.5% sitting)	15.8 ± 0.7 T7	14.0 ± 1.5	10/10	13.0 ± 1.8	304 ± 14	245 ± 12	362 ± 19
Group II (0.5% horizontal)	14.5 ± 0.8 T8	15.6 ± 1.3	10/10	11.0 ± 1.6	327 ± 22	290 ± 15	417 ± 32
Group III (0.75% sitting)	18.7 ± 0.7 T4	14.8 ± 1.2	10/10	6.9 ± 0.8	308 ± 17	294 ± 16	403 ± 28
Group IV (0.75% horizontal)	15.0 ± 0.8 T8	15.8 ± 1.5	8/10	8.0 ± 1.0	329 ± 23	316 ± 19	663 ± 160

The segmental spread of analgesia in the skin was studied by pin-prick using a short-bevel 25-gauge needle with the shoulder as a reference point. Testing was started 4 min after the administration of bupivacaine. Further assessments of analgesia were made at 2-min intervals without moving the patient. After surgery the level of analgesia was studied at intervals of 30 min. Analgesia of only two segments or less was considered the end-point of the study. Analgesia during surgery was described as satisfactory or unsatisfactory. Small doses of fentanyl 0.05–0.1 mg or diazepam 2.5–5 mg were given in the event of unsatisfactory analgesia, restlessness, or shivering. The time between the adminstration of the spinal injection and the first need for postoperative analgesia was recorded. Motor nerve block was assessed using Bromage's score (3–0). The assessments were made by a member of the team other than the anaesthetist who performed the block.

Arterial pressure and heart rate were measured at 5-min intervals during induction and operation, and at intervals of 15 min during recovery. The e.c.g. was monitored continuously.

Analgesia, motor function and sensation were studied in all patients on the following day. Any complaints of headache, dizziness, nausea or vomiting, or difficulty in micturition were noted.

Blood was sampled for measurement of bupivacaine concentration from a large arm vein before administration of bupivacaine and 5, 10, 20 and 30 min after the injection. The concentration of bupivacaine in whole blood was assayed using the gas chromatographic method described by Mather and Tucker (1974).

The statistical significance of differences between the means was tested using Student's *t* test. The criterion of significance was $P \leqslant 0.01$.

RESULTS

Random allocation of patients to treatment groups appeared successful (table I). The maximum spread of pin-prick analgesia during induction of anaesthesia occurred in group III (T4) (table II). Comparing groups III and IV the difference was statistically significant from 8 min after the drug administration; groups III *v.* II after 10 min and between groups III *v.* I after 18 min (fig. 1). There were no statistically significant differences in the maximum spread of analgesia between the other groups. The time to maximum spread of analgesia was approximately 14–16 min in all groups (table II).

When bupivacaine was administered with the patient in a horizontal position, the duration of pin-prick analgesia appeared longer (table II). However, the differences between the groups were not statistically significant.

Analgesia for surgery was considered satisfactory in most cases. Four patients in group I and two in group II received fentanyl i.v. because of pain at the end of surgery. Diazepam or fentanyl were given to lessen restlessness or joint discomfort to a few patients in each group.

The time from spinal block to the need for the first postoperative analgesic was longer when bupivacaine was injected in the horizontal position (table II). However, the differences between the groups were not statistically significant.

At the maximum degree of motor block, most patients reached the maximum score of 3; two in group IV scored 2. The time for the development of maximum motor block was shorter when bupivacaine 7.5 mg ml^{-1} was used (table II). The mean difference between group III and group I was statistically significant.

The duration of motor block could not be assessed precisely in all patients: in five patients in group I and one in group III, the motor function had totally recovered at the end of surgery. This time was taken as motor recovery time in these patients. The mean duration of motor block was longest in group IV (316 ± 19.5 min), but only the difference between groups I and IV was statistically significant (table II).

The changes in arterial pressure and heart rate during anaesthesia are shown in figure 2. The differences between the four groups were not statistically significant. Three patients in group III received ephedrine and infusion of polygeline

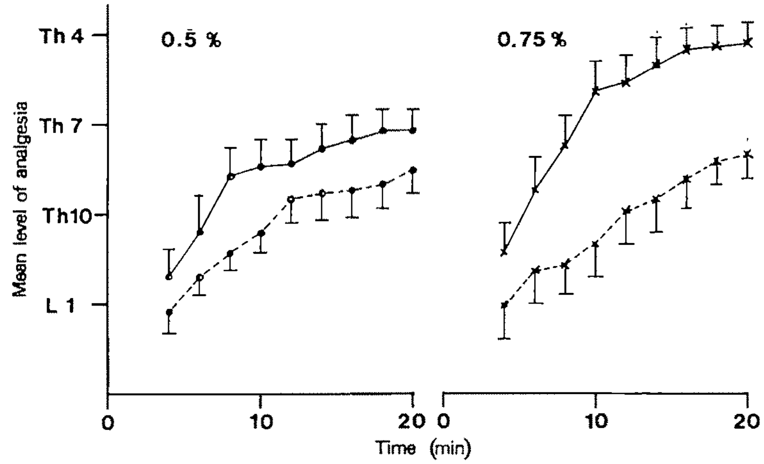

FIG. 1. Mean level of analgesia following intrathecal injection of two different doses of bupivacaine with patients in a sitting or horizontal position. Bars indicating SEM have been drawn only in one direction for easier distinction of the curves. —— = Sitting; --- = Horizontal.

solution because of acute hypotension (systolic pressure less than 90 mm Hg) during induction. One patient in group II and one in group IV received atropine i.v. during induction because of bradycardia (decrease in heart rate more than 30%). The mean decrease in systolic pressure to the lowest values measured during anaesthesia varied from 43 to 64 mm Hg. No statistically significant difference was noticed between the groups. In spite of the decrease in arterial pressure, no signs of shock were manifested.

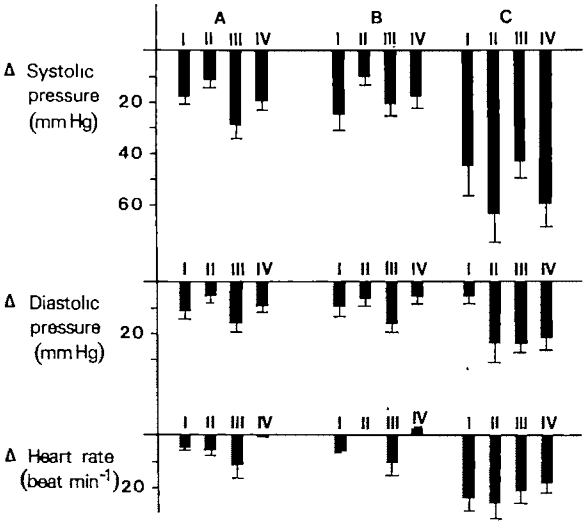

FIG. 2. Mean decrease (± SEM) in arterial pressure and heart rate from preoperative value to the smallest value during induction (A), 20 min after administration of the anaesthetic (B) and during the whole procedure (C). The mean systolic pressure values before operation were 156 ± 10 mm Hg (group I), 160 ± 8 mm Hg (group II), 156 ± 5 mm Hg (group III) and 153 ± 7 mm Hg (group IV).

The frequency of side-effects during the day of surgery is shown in table III. Most complaints occurred in group I: seven patients experienced nausea, two vomited, and four had difficulties with micturition. All these side-effects were recognised as slight and did not disturb the patients on the following day. Brief episodes of headache occurred in some of the patients during surgery and immediately after, but in only one patient was it severe, continuing for about 2 days. The mental state of the patients was good at the time of interview on the following day.

The venous concentrations of bupivacaine are shown in figure 3. The larger dose produced slightly greater blood concentrations, but no significant difference was noticed between the two doses. The maximum individual concentration measured in this study was 0.063 $\mu g\,ml^{-1}$.

TABLE III. *Complications in the period after anaesthesia. The patients were examined on the morning of the first day after operation. *All minor complaints of headaches, irrespective of the cause, were considered*

	Group I	Group II	Group III	Group IV
Headache*	2	1	4	2
Dizziness	1	3	1	2
Nausea	7	5	2	2
Vomiting	2	1	1	—
Micturition problems	4	1	—	—
Backache	—	1	3	—
Hyperalgesia	1	1	1	—
Hyposensation of S1 segment	—	1	—	—
Totals	17	14	12	6

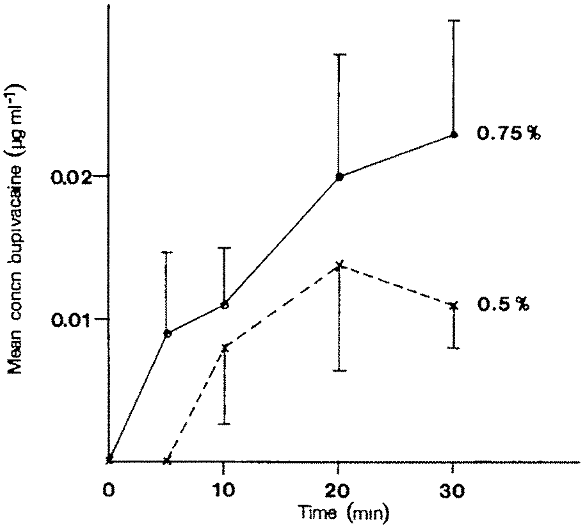

FIG. 3. Mean concentrations of bupivacaine in whole blood ($\mu g\,ml^{-1} \pm$ SEM) in patients injected with 3 ml of 0.75% bupivacaine intrathecally (——) ($n = 7$) or 3 ml of 0.5% bupivacaine intrathecally (---) ($n = 7$). (SEM bars in only one direction.)

DISCUSSION

Three millilitre of isobaric bupivacaine 7.5 mg ml^{-1} administered to induce spinal anaesthesia in patients remaining in the sitting position for 2.5 min after injection of the drug produced a higher level of blockade than the same dose administered in a horizontal position. It also produced a higher level of block than did 3 ml of isobaric bupivacaine 5 mg ml^{-1} administered with the patient in a sitting or horizontal position. The maximum level of analgesia (T8) following intrathecal injection of isobaric bupivacaine 5 mg ml^{-1} with the patient horizontal was almost the same as that found by Chambers, Edström and Scott (1981), using the same dose and position and by Nightingale and Marstrand (1981) using 3–4 ml of isobaric bupivacaine 5 mg ml^{-1} (mean 16.7 mg) in the same position. The level of maximum spread of analgesia in the present study (T7) was the same as that found by Nolte and Stark (1979) when 3 ml of isobaric bupivacaine 5 mg ml^{-1} was administered intrathecally with the patient in the sitting position. However, in their study 2 ml of isobaric bupivacaine both 5 mg ml^{-1} and 7.5 ml administered in the sitting position produced the same level of analgesia, T10. The fact that their patients were moved immediately into a horizontal position might explain the difference in results.

The reason for the different effect of position with isobaric bupivacaine 7.5 mg ml^{-1} and 5 mg ml^{-1} is not known. The time for fixation might be longer when the concentration of local anaesthetic is great (Sato, 1965). It has been assumed that an isobaric bupivacaine solution within the c.s.f. at 37°C would in fact be slightly hypobaric. As the patients in group III remained sitting for 2.5 min, the stronger solution was able to spread more, while in the horizontal patients the solution would tend to stay within the lumbar curve.

There were only small differences between the groups in the duration of pin-prick analgesia. The shortest mean duration was in group I and the patients in this group were the first to need postoperative analgesics. In both the 5 mg ml^{-1} and 7.5 mg ml^{-1} groups, the horizontal position for injection lengthened the time between injection and the first postoperative analgesic. Even excluding a group IV patient who needed no analgesic during the first 24 h, the time difference is impressive (510 ± 47 min in group IV, 403 ± 28 min in group III), although not statistically significant.

As expected, the motor block became complete earlier and lasted longer when the 7.5 mg ml^{-1} solution was used. The reason for the block reaching only category 2 in two patients from group IV is not clear, even in these patients the muscle relaxation was adequate for the surgery.

The haemodynamic changes during induction of analgesia were modest, presumably lessened by the administration of sufficient Ringer solution before and during the induction. Three patients in group III received ephedrine and polygeline infusion because of reduced arterial pressure. The level of pin-prick analgesia was greatest in this group and the sympathetic block is known to extend a few spinal segments higher. However, Chambers, Edström and Scott (1981) found no statistical correlation between height of block and decrease in arterial pressure when isobaric and hyperbaric bupivacaine 5 mg ml^{-1} was used for spinal anaesthesia.

The maximum decrease in systolic arterial pressure during surgery might be regarded as striking. However, the mean systolic values before operation in these elderly patients exceeded 150 mm Hg in each group. The decrease in pressure was always related to the surgical procedure and bleeding. The hypotension was correctable by infusion of blood or another blood volume expander. Arterial hypotension was the main complication during spinal anaesthesia with isobaric bupivacaine 5 mg ml^{-1} in the study of Nightingale and Marstrand (1981). They supposed that it was related to pre-existing dehydration and general debility in elderly patients. No previous dehydration had occurred in our study and all patients were in good general health.

The side-effects during the period after anaesthesia were no longer manifest on the following day. The high frequency of nausea (40%) might be connected with the use of methylmethacrylate bone cement in 70% of the operations (Milliken, Milliken and Marshall, 1976). The postoperative headaches in our study could not be regarded as lumbar puncture headache. They eased within 24 h, except in one suspected case in whom relief from pain was not forthcoming until the 2nd day after operation, following adequate hydration. The neurological sequelae, hyperalgesia and hyposensation of S1 disappeared in a few days. In spite of these side-effects all patients were satisfied with this type of anaesthesia.

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EFFECTS DE LA POSTURE SUR LA DIFFUSION D'UNE RACHIANESTHESIE A LA BUPIVACAINE 0,5 OU 0,75%

RESUME

On a comparé, dans une étude en double aveugle, les effets de la posture sur la diffusion de 3 ml de bupivacaïne isobare à 5 et à 7,5 mg ml^{-1} après injection intrathécale chez 40 sujets soumis à de la chirurgie orthopédique. La diffusion maximale de l'analgésie (D4) est obtenue lorsque 3 ml de bupivacaïne isobare à 7,5 mg ml^{-1} sont administrés à un patient assis au moment de l'injection et pendant 2,5 min après. Le décubitus ou une dose moindre dans l'une ou l'autre position, font remonter l'analgésie en D7–D8. Le bloc moteur des membres inférieurs est bon dans tous les cas. Le décubitus au moment de l'injection, entraîne la plus longue durée moyenne d'analgésie et de bloc moteur, bien qu'il n'y ait pas de différences significatives de durée moyenne entre les groupes. La plus longue durée moyenne d'analgésie à la piqûre d'épingle (329 ± 23 min) est obtenue chez les sujets qui ont reçu de la bupivacaïne 7,5 mg ml^{-1} en décubitus. L'anesthésie et la récupération se sont passées sans incidents chez tous les patients.

DIE WIRKUNG DER KÖRPERHALTUNG AUF DIE AUSBREITUNG EINER SPINALANÄSTHESIE MIT 0,5% ODER 0,75% ISOBAREN BUPIVACAIN

ZUSAMMENFASSUNG

In einer Doppelblindstudie wurde bei 40 Patienten, die sich einem orthopädischen Eingriff zu unterziechen hatten, die Bedeutung der Körperhaltung auf das Wirkspektrum von 3 ml isobaren Bupivacains untersucht. Es Wurden 3 ml isobares Bupivacain 5 mg ml^{-1} mit 3 ml isobarem Bupivacain verglichen. Drei ml isobares Bupivacain 7,5 mg ml^{-1}, das einem Patienten in sitzender Haltung verabreicht wurde, erbrachte während und bis zu 2,5 min nach der Injektion die höchste analgetische Ausbreitung. Eine analgetische Ausbreitung von T7–T8 ergab sich bei horizontaler Körperlage und nach Gabe der kleineren Dosierung in beiden Körperhaltungen. Die motorische Blockade in den Beinen war in allen Fällen gut. Bei horizontaler Körperlage ergab sich zur Zeit der Injektion die längste mittlere Dauer von Analgesie mit motorischem Block, obwohl statistisch keine signifikanten Unterschiede in den mittleren Zeiten zwischen den beiden Gruppen bestanden. Die längste mittlere Dauer der Nadelstichanalgesie (329 ± 23 min) ergab sich bei Patienten, denen in horizontaler Körperlage 7,5 mg ml^{-1} Bupivacain injiziert wurde. Der Anästhesieverlauf und die Erholungsphase waren bei allen Patienten unterschiedlich.

EFECTOS DE LA POSTURA SOBRE LA DISEMINACION DE LA ANALGESIA ESPINAL CON BUPIVACAINA ISOBARICA AL 0,75% O 0,5%

SUMARIO

En un estudio doble-ciego, se comparó los efectos de la postura sobre la diseminación de 3 ml de bupivacaina isobárica 5 y 7,5 mg ml^{-1} después de la inyección intratecal en 40 pacientes sometidos a operaciones ortopédicas. Tres mililitros de 7,5 mg ml^{-1} de bupivacaina isobárica administrados con el paciente en postura sentada durante y por 2,5 min después de la inyección produjeron la mayor diseminación de la analgesia (T4). La postura horizontal y la dosis menor en ambas posturas produjeron una diseminación de la analgesia de T7–8. El bloqueo motor en las piernas fue bueno en todos los casos. La postura horizontal al momento de la inyección resultó en la major duración media de la analgesia y del bloqueo motor, aunque no hubo diferencia alguna de mucho significado desde el punto de vista estadístico en cuanto a duración media entre los grupos. La duración media mayor de la analgesia a la picadura de alfiler (329 ± 23 min) ocurrió en los pacientes cuya inyección se administró en posición horizontal con 7,5 mg ml^{-1} de bupivacaina. El curso de la anestesia y de la recuperación transcurrió sin novedad en todos los pacientes.

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EFFECTS OF EXTRADURAL ANALGESIA AND VAGAL BLOCKADE ON THE METABOLIC AND ENDOCRINE RESPONSE TO UPPER ABDOMINAL SURGERY

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SUMMARY

The effect of thoracic extradural analgesia and vagal blockade on the metabolic and endocrine responses to cholecystectomy was investigated. In comparison with a control group of patients, extradural analgesia and vagal blockade abolished the glycaemic response to surgery but had no effect on the increase in plasma cortisol. Circulating insulin values were significantly decreased in the extradural group of patients, confirming the importance of autonomic innervation in maintaining basal insulin output. There is, at present, no satisfactory local analgesic technique for controlling the endocrine response to upper abdominal surgery.

Kehlet and colleagues have undertaken detailed investigations into the effect of an extensive extradural blockade (S5 to T4) on the metabolic, hormonal and haematological responses to pelvic surgery (for summary see Kehlet, Brandt and Rem, 1980). However, the effect of extradural analgesia on the metabolic response to upper abdominal surgery has received little attention. Bromage, Shibata and Willoughby (1971) found that extradural analgesia for upper abdominal and thoracic surgery abolished the hyperglycaemic response to surgery but had no effect on the increase in plasma cortisol. They postulated that the failure of extradural analgesia to control the hypercortisolaemia was a result of the importance of vagal afferent stimulation in initiating hypothalamic secretion. Therefore, in the present study we have examined the effect of combining thoracic extradural analgesia with vagal blockade on the metabolic and hormonal response to cholecystectomy in patients anaesthetized with halothane.

PATIENTS AND METHODS

Eighteen patients admitted for cholecystectomy were investigated. They were otherwise healthy and had normal liver function tests on admission to hospital. The patients were randomly allocated to receive either extradural analgesia with vagal blockade or to act as control. The nature of the study was explained to the patients and consent obtained for the collection of central venous blood samples.

All patients were premedicated with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 1 h before surgery. On arrival in the anaesthetic room the duration of starvation before surgery was determined and a central venous catheter was inserted percutaneously from an antecubital fossa to permit blood sampling and the administration of i.v. fluids and drugs. After the patient had rested for 10 min a control blood sample was collected and the heart rate and arterial pressure measured.

Those patients who were to receive extradural analgesia were then placed in the lateral position, a catheter was inserted at the T6/7 or T7/8 interspace, and 7–10 ml of 0.5% bupivacaine (35–50 mg) without adrenaline injected to produce sensory blockade to at least T4. Physiological saline solution 750 ml was infused i.v. during this time to maintain the arterial pressure and the same infusion was given to the control group of patients. A second blood sample was obtained and the heart rate and arterial pressure measured.

Anaesthesia was induced with thiopentone, the trachea was intubated following the administration of pancuronium and the lungs were ventilated with 70% nitrous oxide in oxygen supplemented with 0.5% halothane. Ventilation was

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adjusted to maintain an end-tidal carbon dioxide concentration of 4.5–5.0% (Vickers, Datex). Physiological saline solution was administered i.v. during surgery at a rate of 6 ml kg^{-1} h^{-1}; blood replacement was not required, but in three of the nine patients in the extradural group it was necessary to administer methoxamine 2–4 mg i.v. to maintain the mean arterial pressure greater than 60 mm Hg.

In the extradural group of patients vagal blockade was undertaken as soon as the peritoneum was opened. The gastro-oesophageal junction was exposed with gentle retraction and the anterior and posterior vagal trunks identified. Twenty millilitre of 1.5% lignocaine (300 mg) without adrenaline was infiltrated around the trunks. After vagal blockade no further surgery was undertaken for at least 5 min.

Blood samples were collected at 20 min intervals during surgery and were analysed for glucose, free fatty acids (FFA) lactate, cortisol, insulin and haematocrit by methods described previously (Hall et al., 1980; Cooper et al., 1981). Arterial pressure and heart rate were measured at the same time as the blood sample was collected. The adequacy of the extradural analgesia was checked at the completion of surgery. Any patient who was not completely pain-free was excluded from the study.

On the 3rd day after operation the skinfold thicknesses of the patient were measured and the percentage of fat to body weight calculated (Durnin and Rahaman, 1974).

The results are expressed as mean values (±SEM). A two-way analysis of variance was used in both groups to determine the presence of a significant change in mean values with time. A hierarchical two-way analysis of variance was performed to assess the significance of any difference in mean values between the two groups at the same time.

RESULTS

Details of the patients studied are shown in table I. There was no significant difference between the two groups of patients.

The changes in metabolites, hormones and haematocrit are shown in table II. There was a significant increase in blood glucose from 4.45 to 5.57 mmol $litre^{-1}$ ($P<0.01$) after 20 min of surgery in the control group and this hyperglycaemia persisted for the duration of surgery. In the extradural group the glycaemic response to surgery was abolished so that there was a significant difference ($P<0.01$) between the two groups after 20, 40 and 60 min of surgery. There was no significant change in either blood lactate or plasma FFA concentrations in both groups of patients.

TABLE I. *Details (mean ± SEM) of the two groups of patients*

	Control ($n = 9$)	Extradural ($n = 9$)
Age (yr)	49.1±5.6	52.4±5.0
Weight (kg)	64.2±5.9	64.5±4.0
Sex	8F:1M	7F:2M
Starvation before operation (h)	14.7±0.9	13.6±0.8
Estimated blood loss (ml)	231.0±32.0	196.0±16.0
Body fat (%)	36.3±4.8	35.1±1.3

The administration of the fluid load before the induction of anaesthesia caused a significant decrease in haematocrit ($P<0.01$) and was associated with a significant reduction ($P<0.05$) in plasma cortisol and insulin concentrations. With the onset of surgery, however, the hormonal responses differed. Plasma cortisol increased rapidly to 939 nmol $litre^{-1}$ in the control patients and 863 nmol $litre^{-1}$ in the extradural group after 60 min of surgery ($P<0.01$). Insulin concentrations, on the other hand, remained low and after 40 and 60 min of surgery the insulin values in the extradural group were significantly decreased ($P<0.05$) compared with the control patients. The haematocrit declined progressively during the study and there was a 9.6% decrease from control values in both groups after 60 min of surgery.

Changes in heart rate and mean arterial pressure are shown in figure 1. There was no change in heart rate during surgery in the extradural patients, but in the control group the heart rate decreased significantly ($P<0.05$) from the higher control value after 40 and 60 min. Mean arterial pressure decreased significantly in the extradural group after 20 and 40 min ($P<0.01$) and 60 min ($P<0.05$), whereas there was no change in the control group.

DISCUSSION

The results of this study indicate that, in patients undergoing cholecystectomy, the combination of

TABLE II. *Mean (±SEM) concentrations of metabolites, hormones and haematocrit at times: S1 = control, S2 = after extradural and fluid load or fluid load only, S3, S4 and S5 = 20, 40 and 60 min after commencement of surgery respectively. Significance of difference of means from control:* $^{*}P<0.05$; $^{**}P<0.01$ *Differences between groups for each variable shown in final column. n.s. = not significant*

	S1	S2	S3	S4	S5	Control *v.* extradural
Glucose (mmol litre^{-1})						
Control	4.45±0.08	4.62±0.28	5.57±0.27**	5.94±0.36**	5.93±0.38**	$P<0.01$ at S3 S4 and S5
Extradural	4.39±0.11	4.12±0.22	4.47±0.13	4.61±0.16	4.89±0.19	
Lactate (mmol)						
Control	0.77±0.07	0.71±0.10	0.79±0.10	0.77±0.10	0.76±0.10	n.s.
Extradural	0.89±0.12	0.83±0.06	0.92±0.06	0.88±0.12	0.85±0.09	
FFA (mmol litre^{-1})						
Control	1.26±0.23	1.10±0.17	0.97±0.05	1.06±0.05	1.08±0.07	n.s.
Extradural	0.94±0.17	0.98±0.21	0.83±0.19	0.93±0.14	0.98±0.16	
Cortisol (nmol litre^{-1})						
Control	379±58	278±50*	654±70**	958±44**	939±65**	n.s.
Extradural	372±56	236±36*	564±52*	834±65**	863±60**	
Insulin (mu. litre^{-1})						
Control	6.00±1.0	3.50±0.9*	3.30±0.8**	3.50±0.5**	3.90±0.7**	$P<0.05$ at S4 and S5
Extradural	5.60±0.8	3.20±0.4*	2.80±0.3**	2.50±0.1**	2.40±0.1**	
Haematocrit (%)						
Control	39.40±0.8	37.50±1.1**	36.80±0.8**	36.10±1.1**	35.60±0.8**	n.s.
Extradural	38.40±0.9	36.30±1.1**	36.00±0.8**	35.30±0.9**	34.70±0.8**	

thoracic extradural analgesia with vagal blockade inhibits the hyperglycaemia but not the hypercortisolaemia of surgery. This technique, therefore, offers no hormonal or metabolic advantages over extradural analgesia alone for abdominal surgery. This finding was surprising in view of the importance attached to vagal afferent stimulation by Bromage, Shibata and Willoughby (1971). There are two important factors which may have been responsible for the failure of vagal blockade to inhibit the cortisol response.

First, it is important to note that no attempt was made to ascertain the adequacy of vagal blockade. Without the use of objective tests of vagal integrity, such as the stimulation of acid secretion by insulin-induced hypoglycaemia (Baron, 1978), it is not possible to assess the efficacy of this procedure. We considered, however, that if this technique was to be of any practical value then it must be undertaken with minimal disruption to surgery. Furthermore, the administration of insulin is clearly inappropriate in a metabolic study. Although the surgeons undertaking the vagal blockade were all experienced at identifying the vagal trunks and their branches, it was surprising to find that in none of the nine patients studied was the cortisol response either delayed or reduced.

Second, some autonomic afferent stimulation undoubtedly occurred during the retraction and dissection necessary to expose the vagal trunks and this was possibly sufficient to initiate the hormonal response. Once the endocrine changes are established, there is no evidence that afferent blockade is of value in inhibiting the increased cortisol secretion. The inability of neuronal blockade to alter an established endocrine response reflects the perturbation of the normal control mechanisms of hormonal secretion found during surgery, for example the continuing secretion of ACTH in the presence of increased plasma cortisol concentrations (Thoren, 1974).

High-dose fentanyl anaesthesia was more effective in controlling the metabolic response to upper abdominal surgery than the extradural analgesia and vagal blockade used in the present study (Cooper et al., 1981). The administration of fentanyl 50 μg kg^{-1} at the induction of anaesthesia delayed the increase in plasma cortisol for 60 min and the hyperglycaemia for 120 min in patients

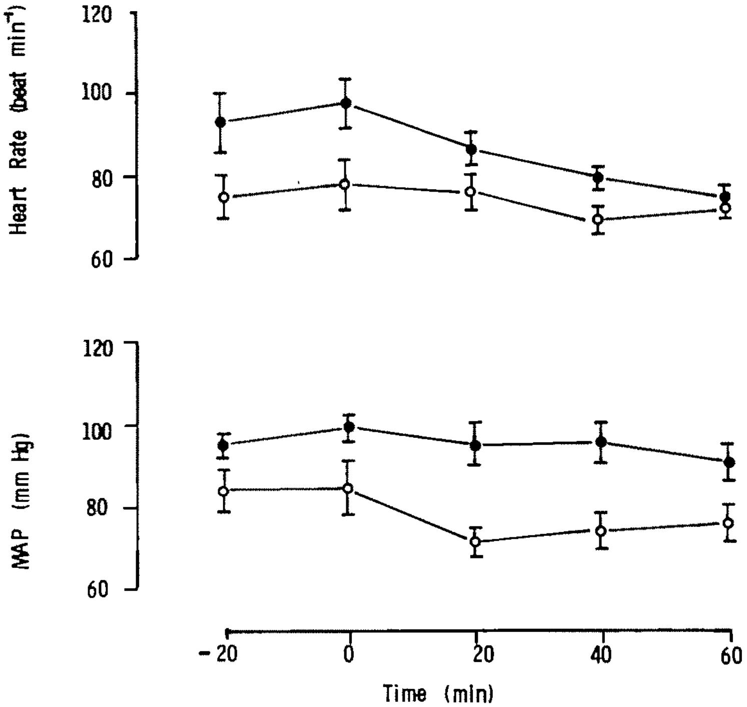

FIG. 1. Mean (± SEM) heart rate and mean arterial pressure (MAP) in control group of patients (closed circles) and extradural group of patients (open circles).

undergoing gastric surgery. Severe respiratory depression occurred in all patients in the period after operation and the authors could not recommend the use of high-dose fentanyl anaesthesia for upper abdominal surgery.

It is well known that there is a failure of insulin secretion in response to the hyperglycaemia of surgery and this is usually considered to be a result of the α-adrenergic inhibitory effects of the circulating catecholamines (Allison, 1971). Autonomic innervation of the pancreas also exerts important control over insulin secretion (Woods and Porte, 1974). Halter and Pflug (1980) have demonstrated recently that adrenergic neuronal input to the pancreas is essential for the maintenance of basal insulin secretion. They observed that high spinal anaesthesia (T2–T6) was associated with a reduction in the insulin response to i.v. glucose and arginine in the presence of a decrease in circulating noradrenaline and adrenaline values. In contrast, during low spinal anaesthesia (T9–T12), there was no suppression of the insulin response to i.v. glucose or of circulating catecholamines. Furthermore, vagal efferent blockade also inhibits insulin secretion (Porte et al., 1973). Therefore, the occurrence of significantly smaller plasma insulin values in those patients who received extradural analgesia and vagal blockade (table II) is in keeping with the existing knowledge of the influence of autonomic factors on pancreatic islet cell function.

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EFFECT DE L'ANALGESIE PERIDURALE ET DU BLOC VAGAL SUR LA RESPONSE METABOLIQUE ET ENDOCRINIENNE A LA CHIRUGIE DE L'ETAGE SUS-MESOCOLIQUE

RESUME

On a étudié les effets de l'analgésie péridurale dorsale et du bloc vagal sur la réponse métabolique et endocrinienne à la cholecystectomie. Si l'on compare les résultats à ceux d'un groupe témoin, l'analgésie péridurale et le bloc vagal abolissent la réponse glycémique à la chirurgie mais sont sans effet sur la cortisolémie. Les valeurs d'insuline circulante sont significativement plus basses dans le groupe des patients ayant reçu une péridurale, ce qui confirme l'importance de l'innervation végétative dans le maintien de la libération basale d'insuline. Il n'existe à ce jour aucune technique d'analgésie loco-régionale satisfaisante pour contrôler la réponse endocrine à la chirurgie de l'étage sus-mésocolique.

DIE WIRKUNG EINER EPIDURALANALGESIE UND EINER VAGALBLOCKADE AUF DIE METABOLISCHE UND ENDOKRINOLOGISCHE REAKTION AUF OBERBAUCHEINGRIFFE

ZUSAMMENFASSUNG

Die Wirkung einer thorakalen Epiduralanalgesie und einer vagalen Blockade auf die metabolische und endokrinologische Reaktion nach Cholecystektomie wurde untersucht. Im Vergleich zur Kontrollgruppe verhinderte die Epiduralanalgesie und die vagale Blockade die glykämische Reaktion auf den chirurgischen Eingriff, hatte jedoch keinen Einfluss auf die Zunahme des Plasmacortisols. Die zirkulierenden Insulinwerte fielen in der Epiduralgruppe signifikant ab und bestätigten dadurch die Bedeutung einer unabhängigen Innervation durch Aufrechterhaltung des basalen Insulin-Output's. Bis heute gibt es noch keine befriedigende Lokalanalgesietechnik zur Kontrolle der endokrinen Reaktion auf chirurgische Oberbaucheingriffe.

EFECTOS DE LA ANALGESIA EXTRADURAL Y DEL BLOQUEO VAGAL SOBRE LA RESPUESTA METABOLICA Y ENDOCRINA A LA CIRUJIA ABDOMINAL SUPERIOR

SUMARIO

Se investigó el efecto de la analgesia extradural torácica y del bloqueo vagal sobre la respuesta metabólica y endocrina a la colecistectomía. En comparación con un grupo de control de pacientes, la analgesia extradural y el bloqueo vagal abolieron la respuesta glicémica a la cirujía pero no tuvieron ningún efecto sobre el aumento del cortisol del plasma. Los valores de la insulina circulante disminuyeron de manera significativa en el grupo extradural de pacientes, lo que confirma la importancia de la inervación para mantener la producción de insulina basal. No existe, en la actualidad, ninguna técnica analgésica local satisfactoria para controlar la respuesta endocrina a la cirujía abdominal superior.

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POSTOPERATIVE GLUCOSE TOLERANCE DURING EXTRADURAL ANALGESIA

F. P. BUCKLEY, H. KEHLET, N. S. BROWN AND D. B. SCOTT

SUMMARY

Thirteen patients undergoing lower abdominal gynaecological surgery were allocated to general anaesthesia (halothane and nitrous oxide) or general anaesthesia plus extradural analgesia (T8–S5). I.v. glucose tolerance tests were performed on the day before surgery and 8 h after skin incision. All patients having extradural analgesia (T8) were pain-free following surgery. Extradural analgesia blocked the hyperglycaemic response to surgery but not the late postoperative cortisol response, although values were significantly less than in the group receiving general anaesthesia alone. Impairment of glucose tolerance and of the insulin response to the glucose load in the period after operation were not influenced by extradural analgesia and this may have resulted from insufficient inhibition of the stress-induced release of catecholamines or cortisol, or both, or from blockade of stimulatory efferent sympathetic pathways to pancreatic islets.

Surgery under general anaesthesia produces changes in glucose homeostasis with hyperglycaemia, glucose intolerance and impaired release of insulin (Allison, Tomlin and Chamberlain, 1969; Aarimaa et al., 1974; Wright, Henderson and Johnston, 1974). During operation, anaesthetic agents may contribute to the decrease in glucose tolerance (Dundee, 1956; Kaniaris et al., 1975) and the impairment of insulin release (Merlin, Samuelson and Schalch, 1971; Gingerich, Wright and Paradise, 1974), but such changes are also found in the postoperative period after the anaesthetic agents have been discontinued (Aarimaa et al., 1974; Wright, Henderson and Johnston, 1974). Extradural blockade for surgery and postoperative analgesia has been shown to diminish (Bromage, Shibata and Willoughby, 1971; Brandt et al., 1976) or abolish (Engquist et al., 1977) the hyperglycaemic response to surgery and to prevent the impairment of glucose tolerance and diminished release of insulin observed during operation (Houghton et al., 1978; Jensen et al., 1980).

The present study was designed to investigate the ability of extradural analgesia to ameliorate the glucose intolerance and impairment of insulin release following operation at a time when the influence of general anaesthetic agents upon these factors should be of minor importance.

PATIENTS AND METHODS

The patients were premenopausal women within 10% of their ideal body weight, who had neither a personal nor a family history of diabetes, who were not taking any hormonal preparations and were to undergo lower abdominal laparotomy for gynaecological complaints. All patients gave informed consent for the procedure and were randomly allocated to receive either anaesthesia with thiopentone, halothane and nitrous oxide (group A, seven patients) or thiopentone, halothane and nitrous oxide anaesthesia plus extradural blockade from S5 to T8 with 0.5% plain bupivacaine (group B, six patients). Mean ages (±SEM) in groups A and B were 35.7±3.7 yr and 38.3±2.5 yr (n.s.), respectively. Mean weights were 66.3±2.8 kg and 60.6±4.0 kg (n.s.), respectively. Mean durations of anaesthesia were 97±3 min and 103±6 min (n.s.), and of operation 71±6 min and 58±6 min ($P < 0.05$), in groups A and B respectively.

On the day before surgery, at 17.00 h and after an 8-h fast, a 25-g i.v. glucose tolerance test (i.v. g.t.t.) was performed (Samols and Marks, 1965).

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In all patients premedication consisted of diamorphine 5 mg i.m. and atrophine 0.6 mg i.m.

In group A, anaesthesia was induced with thiopentone 300–400 mg, neuromuscular blockade achieved with tubocurarine 30–40 mg and the trachea intubated. Anaesthesia was maintained with nitrous oxide in oxygen with flows of 3 and 1.5 litre respectively, plus 0.5% halothane, into a closed circle system with carbon dioxide absorption. Ventilation of the lungs was controlled with a volume-cycled respirator at an expired minute volume of $100 \, \text{ml} \, \text{kg}^{-1} \, \text{min}^{-1}$. At the completion of surgery, the neuromuscular blockade was antagonized with atropine 1.2 mg and neostigmine 2.5 mg and analgesia maintained thereafter with diamorphine 2.5–5 mg i.m. as necessary.

In group B, an extradural catheter was placed at L3–4 via a midline insertion and analgesia induced with 0.5% bupivacaine plain in a dose sufficient to achieve a block to at least T8 for the period of surgery. General anaesthesia was then induced with thiopentone 200–300 mg and maintained with nitrous oxide in oxygen, 3 and 1.5 litre respectively plus 0.5% halothane into a closed circle system with carbon dioxide absorption. The patients breathed spontaneously via a mask. After the operation, satisfactory analgesia was achieved in group B by maintaining the extradural blockade at least at T8 with repeated doses of 0.5% bupivacaine given at approximately 90-min intervals. Any patient in group B who felt abdominal pain or in whom the block regressed below T8 was excluded from the study.

During operation, all patients received i.v. fluids at a rate of $750 \, \text{ml} \, \text{h}^{-1}$ of physiological saline; blood loss, which in no case exceeded 300 ml, was replaced with twice its volume of physiological saline. After operation, all patients received physiological saline approximately $120 \, \text{ml} \, \text{h}^{-1}$. No patient received any vasopressor drugs or sympathomimetic amine.

Blood samples were taken before anaesthesia, during anaesthesia but before the skin incision and at intervals after the skin incision for a period of 8 h. Eight hours after the skin incision, about 6–8 h after the completion of surgery and general anaesthesia, and at approximately the same time of day (17.00 h) as the preoperative i.v. g.t.t., a further i.v. g.t.t. was performed.

All blood samples for hormone estimations were drawn from a central venous catheter, immediately centrifuged and the supernatant plasma was frozen until assayed. Plasma insulin concentration was measured by a modification of a double antibody radioimmunoassay technique (Hunter, Willoughby and Strong, 1968). Plasma cortisol concentration was measured by a competitive protein-binding technique (Kehlet, Binder and Engbaek, 1974). Blood glucose samples were analysed by a glucose oxidase technique.

The preoperative and postoperative i.v. g.t.t. were analysed by obtaining semi-logarithmic plots of blood glucose concentrations against time and calculating the glucose assimilation coefficient (K) as described by Samols and Marks (1965). The insulin response to i.v. g.t.t. was expressed as a maximal response (that is the maximal insulin concentration obtained during the course of the i.v. g.t.t. minus the basal insulin concentration, before injection of glucose) and total insulin response (the area under the curve of insulin against time from 10 to 40 min after i.v. glucose). Student's t test for paired and unpaired data was used to assess significance: $P<0.05$ was considered significant.

RESULTS

Glucose (fig. 1)

Before anaesthesia and during anaesthesia, but before surgery, blood glucose concentrations in both groups A and B were within normal limits and were comparable. In group A, blood glucose concentration increased 30 min after incision to values significantly ($P<0.01$) greater than the values before operation and remained significantly increased throughout the period of the study. In group B, other than a transient decrease 30 min after incision, blood glucose concentration was not significantly different from preoperative values during the study. There were significant differences between blood glucose concentrations in the two groups at all intervals after incision.

Cortisol (fig. 1)

Induction of anaesthesia produced no changes in plasma cortisol concentrations in either group. Cortisol concentration had increased significantly ($P<0.001$) in group A by 1 h after the incision and remained significantly increased throughout the study. In group B plasma cortisol concentration did not increase until 2 h after incision and remained significantly increased throughout the remainder of the study. Plasma cortisol concentration was significantly less in group B at 1, 2, 4 and 6 h after incision, when compared with group A.

Insulin (fig. 1)

Plasma insulin concentration decreased in both groups following the induction of anaesthesia, returning to preoperative values by 90 min after the incision. Thereafter, the insulin concentrations were similar to the preoperative values throughout the investigation. While the differences between groups A and B at 1, 2 and 8 h after incision are statistically significant ($P < 0.05$), the mean concentrations are within the range of normal fasting values and thus the difference is probably not clinically significant.

Glucose tolerance (table I)

Before operation blood glucose concentration was normal and similar in both groups. In group A, the fasting blood glucose value after surgery was significantly greater than the preoperative value and was significantly greater than the fasting blood glucose concentration in group B following surgery. Fasting blood glucose concentrations in group B were similar before and after operation. The mean K values before operation in groups A and B were not different. Mean K values after operation were significantly less ($P < 0.05$) in both groups when compared with preoperative values. There was no significant difference between postoperative K values in the two groups.

Insulin response (table II)

Before operation, basal values of insulin and both the maximum and total insulin responses to i.v. g.t.t. were similar in both groups. Following operation the basal concentrations of insulin were not different from the preoperative values in either group and were similar in both groups. After operation the maximal insulin response decreased significantly in both group A ($P < 0.05$) and group B ($P < 0.01$). Total insulin response also decreased in both groups, significantly in group B ($P < 0.01$) but not significantly in group A. Postoperative values for maximal and total insulin response were not significantly different between the groups.

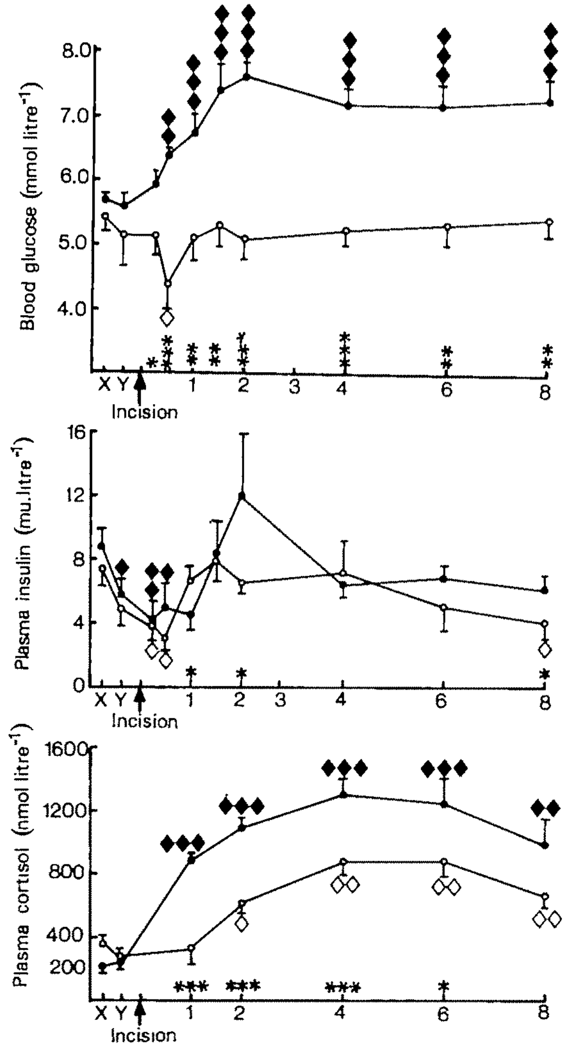

FIG. 1. Mean (±SEM) blood glucose (mmol litre^{-1}), plasma insulin (mu. litre^{-1}) and plasma cortisol (nmol litre^{-1}) concentrations before anaesthesia (X), during anaesthesia but before incision (Y) and at intervals (h) after incision. ● = Group A (general anaesthesia); ○ = group B (general anaesthesia and extradural block). Significant differences from before anaesthesia (X) values: Group A—◆ $P<0.05$, ◆◆ $P<0.01$, ◆◆◆ $P<0.001$; Group B—◇ $P<0.05$, ◇◇ $P<0.01$, ◇◇◇ $P<0.001$. Significant differences between groups A and B: *$P<0.05$, **$P<0.01$, ***$P<0.001$.

DISCUSSION

Our results show that, despite the ability of extradural analgesia to abolish the hyperglycaemic response during and following surgery, such analgesia did not prevent the impairment of either glucose tolerance or insulin release in the

TABLE I. *Fasting blood glucose concentrations (mmol litre^{-1}) ± SEM before i.v. glucose tolerance test and glucose disposal rate* (K) *± SEM of i.v. glucose tolerance test, before operation and 8 h after skin incision. Group A = general anaesthesia; group B = general anaesthesia plus extradural blockade. *Mean of two samples*

		Before operation		8 h after skin incision	
	Patient no.	Fasting* blood glucose (mmol litre^{-1})	K	Fasting* blood glucose (mmol litre^{-1})	K
Group A					
	1	5.25	0.79	7.3	0.77
	2	5.35	0.58	7.9	0.73
	3	5.15	0.77	7.8	0.53
	4	5.95	1.07	5.6	0.54
	5	6.15	0.71	7.8	0.62
	6	5.15	3.65	6.5	1.17
	7	5.60	0.80	8.1	0.50
	Mean	5.48	1.2	7.30	0.69
	SEM	0.10	0.4	0.24	0.10
	Preop. *v.* postop.			$P<0.01$	$P<0.05$
Group B					
	1	5.25	1.64	6.05	0.79
	2	5.10	1.21	4.75	1.03
	3	5.35	0.86	4.50	0.63
	4	5.30	0.90	5.55	0.83
	5	5.85	1.44	6.45	0.70
	6	4.25	0.76	5.03	0.70
	Mean	5.18	1.14	5.39	0.78
	SEM	0.15	0.15	0.21	0.06
	Preop. *v.* postop.			n.s.	$P<0.05$
Group A *v.* group B		n.s.	n.s.	$P<0.001$	n.s.

period after operation. These results are in contrast to studies performed during surgery (Houghton et al., 1978; Jensen et al., 1980) in which extradural analgesia prevented the impairment of glucose tolerance. The explanation of the differences between the studies during and after operation is not known, but differences in anaesthetic technique and the extent of sensory blockade, which may influence the release of such hormones such as cortisol (Engquist et al., 1977) or catecholamines, may be of importance.

In the studies carried out during surgery an extradural block was the sole technique of anaesthesia in the extradural group of patients, whereas in the present study the extradural group also received general anaesthetic agents, thiopentone and halothane. Thiopentone has been shown to impair glucose tolerance (Dundee, 1956; Kaniaris et al., 1975) and halothane impairs the release of insulin in response to hyperglycaemia (Merin, Samuelson and Schalch, 1971; Gingerich, Wright and Paradise, 1974) and may thus impair glucose tolerance also. However, it is difficult to attribute the differences between the intraoperative and postoperative studies to anaesthetic agents, as the postoperative study was performed 6 or 7 h after the discontinuation of those agents.

The inhibition of the cortisol response to surgery by extradural analgesia may be an important factor in the prevention of the impairment of glucose tolerance, as physiological hypercortisolaemia results in a progressive decrease in glucose clearance (Shamoon, Soman and Sherwin, 1980). Although in this study the extradural group had significantly lower cortisol concentrations than the general anaesthesia group, the cortisol concentrations in the extradural group did increase from about 300 nmol litre^{-1} to 800 nmol litre^{-1} by 4–6 h after skin incision, and thus may have contributed to the impaired glucose tolerance at 8 h after skin incision. However, the hypercortisolaemia does not explain the impairment of insulin release in response to a glucose challenge (Shamoon, Soman and Sherwin,

TABLE II. *Insulin response (mu. litre^{-1}) to i.v. glucose tolerance test before operation and 8 h after skin incision. (Max. response = maximal concentrations reached minus basal concentrations before injection of glucose. Total response is area under the curve of insulin against time from 5 to 40 min after the i.v. glucose tolerance test)*

	Patient no.	Before operation Basal values	 Max. response	 Total response	8 h after skin inclusion Basal values	 Max. response	 Total response
Group A							
	1	4.1	41.5	770	3.8	14.0	380
	2	4.8	26.4	778	7.4	13.8	627
	3	5.3	34.6	1154	4.5	13.1	323
	4	7.6	34.6	815	5.3	30.0	736
	5	7.1	49.7	920	7.2	68.0	1471
	6	20.5	175.5	3572	10.1	57.1	1832
	7	5.5	56.1	1298	6.3	14.7	749
Mean		7.8	61.4	1329	6.3	30.0	845
SEM		2.1	19.4	381	0.8	8.7	221
Preop. *v.* postop.					n.s.	$P<0.05$	n.s.
Group B							
	1	9.0	47.0	898	7.6	21.2	390
	2	7.1	88.9	1480	3.5	40.0	888
	3	3.3	45.5	887	3.0	39.4	807
	4	4.3	34.4	715	4.3	21.5	468
	5	4.8	72.4	1338	3.0	16.3	398
	6	3.8	45.0	830	2.6	12.0	380
Mean		5.3	55.5	1024.7	4.0	25.1	605.2
SEM		0.9	8.4	125.7	0.7	4.8	90.4
Preop. *v.* postop.					n.s.	$P<0.01$	$P<0.01$
Group A *v.* group B		n.s.	n.s.	n.s.	$P<0.05$	n.s.	n.s.

1980). The cortisol response to surgery was abolished in one of the intraoperative studies of glucose tolerance during extradural block (Jensen et al., 1980); in the other (Houghton et al., 1978) an increase in cortisol concentration was seen, but this increase may have been present for too short a time to influence glucose metabolism (Shamoon, Soman and Sherwin, 1980).

Our results may have been affected by altered catecholamine secretion as both insulin secretion (Porte and Robertson, 1973) and glucose clearance (Rizza et al., 1979) are inhibited by catecholamines. However as neither we, nor other workers, have measured catecholamine concentrations in patients recovering from surgery with extradural analgesia this remains conjecture. Paradoxically, extradural analgesia may, by producing a neurogenic blockade of the efferent adrenergic pathways to the pancreas, contribute to the decrease in glucose tolerance and insulin release as baseline adrenergic input is important in maintaining normal pancreatic islet function (Halter and Pflug, 1980).

In conclusion, extradural analgesia, despite blocking the hyperglycaemic response and partially inhibiting the cortisol response to surgery, did not prevent the impairment of glucose tolerance, of insulin secretion in response to a glucose load, in the period after operation. These findings are contrary to those found in studies undertaken during operation and are possibly related to incomplete inhibition of stress-induced catecholamine release or cortisol release, or both, or to a blockade of the stimulatory efferent pathways to the pancreatic islets.

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TOLERANCE POST-OPERATOIRE AU GLUCOSE AU COURS DE L'ANALGESIE PERIDURALE

RESUME

Treize patientes soumises à des actes de chirugie gynécologique de la partie infériere de l'abdomen ont reçu soit une anesthésie générale (halothane et protoxyde d'azote) soit une anesthésie générale associée à une analgésie péridurale (D8–S5). Des tests de tolérance au glucose intraveineux ont été faits la veille de l'intervention et 8 h après l'incision de la peau. Aucune des patientes ayant une analgésie péridurale (D8) ne souffrait aprés l'acte chirurgical. L'analgésie péridurale a bloqué la réponse hyperglycémique à la chirurgie mais pas la réponse post-opératoire tardive du cortisol, bien que les valeurs de la cortisolémie aient été significativement plus basses que dans le groupe ayant reçu une anesthésie générale seule. Les altérations de la tolérance au glucose et de la réponse insulinique à une charge en glucose dans la période post-opératoire n'ont pas été influencées par l'analgésie péridurale, et ceci peut avoir été dû à une insuffisance d'inhibition de la libération de catécholamines ou de cortisol (voire des deux) induite par le stress, ou à un blocage des voies sympathiques efferentes stimulatrices des îlots pancréatiques.

POSTOPERATIVE GLUKOSETOLERANZ WÄHREND EINER EPIDURALANALGESIE

ZUSAMMENFASSUNG

Dreizehn Patienten mit einer gynäkologischen Unterleibsoperation wurden für eine Allgemeinnarkose (Halothane und Stickoxydul) bzw. für eine Allegemeinnarkose plus Epiduralanalgesie (T8–S5) ausgewählt. Ein Tag präoperativ und 8 Stunden nach der Laparotomie wurden i.v. Glukosetests durchgeführt. Alle Patienten mit einer Epiduralanalgesie (T8) waren nach der Operation schmerzfrei. Die Epiduralanalgesie hatte die hyperglykämische Antwort auf den chirurgischen Eingriff blockiert, aber nicht die spätere postoperative Cortisol-Freisetzung, obwohl die Konzentrationen signifikant niedriger waren als in der Gruppe mit Allgemeinnarkose. Die Verschlechterung der Glukosetoleranz und der Insulinantwort auf die Glukosebelastung in der postoperativen Phase wurde nicht beeinflusst durch die Epiduralanalgesie. Dies kann auf die insuffiziente Hemmung der stressinduzierten Freisetzung von Katecholaminen, oder von Cortisol, oder von beiden, oder auch auf eine Blockade der stimulatorischen efferenten sympathetischen Verbindung zum Pankreas zurückzuführen sein.

TOLERANCIA POSTOPERATORIA A LA GLUCOSA DURANTE LA ANALGESIA EXTRADURAL

SUMARIO

Se administró a trece pacientes sometidas a cirujía ginecológica del abdomen bajo una anestesia general (halotano) y óxido nitroso o una anestesia general más analgesia extradural (T8–S5). Se llevaron a cabo ensayos sobre tolerancia a la glucosa i.v. el día anterior a la operación quirúrgica y después de una incisión de la piel. Todas las pacientes que tuvieron la analgesia extradural (T8) no sufrieron ningún dolor después

de la operación. La analgesia extradural bloqueó la respuesta hiperglicémica a la cirujía pero no asi la respuesta postoperatoria tardía al cortisol, aunque los valores fueron significantemente menores que en el grupo que recibió la anestesia general solamente. El deterioro de la tolerancia a la glucosa y de la respuesta de la insulina a la carga de glucosa en el periodo después de la operación no fueron influenciados por la analgesia extradural y esto tal vez resultó de la insuficiente inhibición de la liberación inducida por presión de la catecolaminas o del cortisol, o de ambos, o del bloqueo de los senderos simpáticos eferentes estimulatorios a las isletas pancreáticas.

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TOURNIQUET-INDUCED HYPERTENSION

R. D. KAUFMAN AND L. F. WALTS

SUMMARY

The anaesthetic records of 600 patients undergoing lower limb surgery were reviewed to determine the frequency of intraoperative arterial hypertension (defined as a 30% increase in either systolic or diastolic pressure compared with the first pressure recording after incision). The overall frequency of hypertension during operation in 500 patients to whom a tourniquet was applied during surgery was 11%. The probability of hypertension was increased if the patient was elderly, had cardiac enlargement shown by x-ray or e.c.g., or had nitous oxide and narcotic anaesthesia. Pre-existing hypertension, increased serum creatinine concentration, anaemia, or treatment with antihypertensives, diuretics, or steroids were not strongly associated with intraoperative hypertension. A control group of 100 patients undergoing hip surgery without application of a tourniquet exhibited hypertension in 1% of cases.

While administering anaesthesia for orthopaedic operations on the lower limb, the authors noted that a significant number of patients developed alarming increases in arterial pressure. This hypertension seemed to follow inflation of a thigh tourniquet and, even more striking, the pressure usually returned to near normal values shortly after the tourniquet was released. To determine the frequency of hypertension and possible predictors of the development of hypertension, we conducted a retrospective review of 600 anaesthetics given to patients undergoing leg operations.

METHODS

Records were obtained for 600 patients having operations on the lower limb, all performed in 1978. Five hundred patients had operations necessitating the use of a thigh tourniquet. The additional 100 patients (control group) underwent total and surface hip arthroplasty that did not necessitate the use of a tourniquet. All operations were carried out by the same group of surgeons, and took place in the same operating room. Anaesthesia was administered, in nearly every case, by the same team. The preoperative evaluation of these patients was reviewed to determine the presence of cardiovascular or renal disease and general information such as age, sex and race. The type of anaesthesia and, in the case of general anaesthesia, the agents used were recorded. These data were correlated with the occurrence of hypertension. Statistical significance of continuous variables was determined by applying Student's *t* test. The Fisher exact test (two-tail) was applied to dichotomous variables.

The arterial pressures measured on the day of admission to the hospital, immediately before the induction of anaesthesia and following the incision were noted. During the operation the pressure was recorded at 5-min intervals. Since arterial pressure may vary before operation (because of anxiety) and may be decreased after the induction of anaesthesia, the first pressure reading obtained after the operation was in progress was selected as a baseline; this was the first reading taken after inflation of the tourniquet, or the first reading after incision. Since incision usually followed inflation of the tourniquet by 1 or 2 min, the first pressure measurement after tourniquet inflation and after incision were usually the same measurement. Hypertension was defined as a 30% increase from baseline in either the systolic or diastolic pressure.

RESULTS

In the tourniquet group, various anaesthetics were used: halothane (150 patients), enflurane (117), nitrous oxide and narcotic (44), regional block (153) and more than one of these in 34 patients. These last 34 patients had undergone attempted regional block which failed or did not

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last for an adequate time or was supplemented with nitrous oxide. Fifty-five of the patients (11%) became hypertensive during operation.

Anaesthesia for the control group was halothane (56 patients); enflurane (20), nitrous oxide and narcotic (19), regional block (two), other (three). One patient became hypertensive during operation.

A multivariate analysis by logistic regression was made on all of the risk factors. This analysis determined type of anaesthesia, cardiac enlargement and age to be the only significant factors. The hypertensive patients were older, had evidence of cardiac enlargement on e.c.g. or chest x-ray, and were more likely to have received nitrous oxide–narcotic anaesthesia. Table I summarizes the effect and interaction of the three risk factors. The probability of hypertension varies from 0.01 to 0.67, depending upon the combination of these risk factors. Pre-existing hypertension, a history of angina or myocardial infarction, a history of congestive heart failure, an increase in plasma creatinine, a decrease in serum potassium, anaemia or treatment with antihypertensive, diuretic or steroid drugs were all not significant. There was no difference in respect of weight or race and no significant difference in the volume of fluid administered during operation to hypertensive and non-hypertensive patients.

Using the coefficients of the logistic regression determined from the tourniquet group, the control group would have been expected to exhibit hypertension in 17 of the cases. However, only one patient of the control group met the criteria for post-incision hypertension.

The figure shows the distribution of baseline and greatest arterial pressures of the patients having hypertension. Note that seven patients had systolic pressures greater than 190 mm Hg, the highest value found on our records. The time to achieve the highest pressure in each case (latency) was often greater than 1 h.

DISCUSSION

The presence of the tourniquet appears to be the main precipitating factor in the hypertension noted. It is unlikely that a light level of anaesthesia could be incriminated, since the controls had equally traumatic procedures but did not become hypertensive. In addition, the long latency of the hypertension is not consistent with a light level of anaesthesia. In patients anaesthetized with potent vapours the level of anaesthesia would be expected to be deeper with time as the alveolar concentrations approached inspired concentration (Eger, 1974). Inspired concentrations were increased or additional amounts of a narcotic administered in response to the hypertension in some cases. Thus, the true frequency and severity of hypertension may have been underestimated.

The long latency of the hypertension is also inconsistent with a direct haemodynamic effect of the tourniquet. The leg is exsanginated with a rubber bandage before the tourniquet is inflated, causing a transfusion of blood to the central circulation. However, this transfusion, or any change of peripheral vascular resistance secondary to the tourniquet, should have a prompt effect. Bradford (1969) has shown that an increase in systolic pressure following placement of a tourniquet on one lower limb occurs within 15 min of cuff inflation, and averages only 18 mm Hg increase in pressure.

A mechanism compatible with a long latency is that proposed for tourniquet pain during spinal

TABLE I. *Probability of hypertension as a function of anaesthesia, age and presence of cardiac enlargement*

	Regional		Halothane		Enflurane		Other		Balanced	
Cardiac enlargement	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Age (yr)										
10–19	0.01	0.04	0.05	0.13	0.07	0.18	0.16	0.35	0.18	0.37
20–29	0.02	0.05	0.06	0.15	0.09	0.21	0.19	0.39	0.20	0.42
30–39	0.02	0.06	0.07	0.18	0.10	0.24	0.12	0.44	0.24	0.46
40–49	0.02	0.07	0.08	0.20	0.12	0.27	0.25	0.48	0.27	0.50
50–59	0.03	0.08	0.10	0.23	0.14	0.31	0.29	0.52	0.31	0.55
60–69	0.03	0.09	0.12	0.27	0.16	0.35	0.32	0.57	0.34	0.59
70–79	0.04	0.11	0.14	0.30	0.19	0.39	0.36	0.61	0.39	0.63
80+	0.05	0.12	0.16	0.34	0.22	0.44	0.41	0.65	0.43	0.67

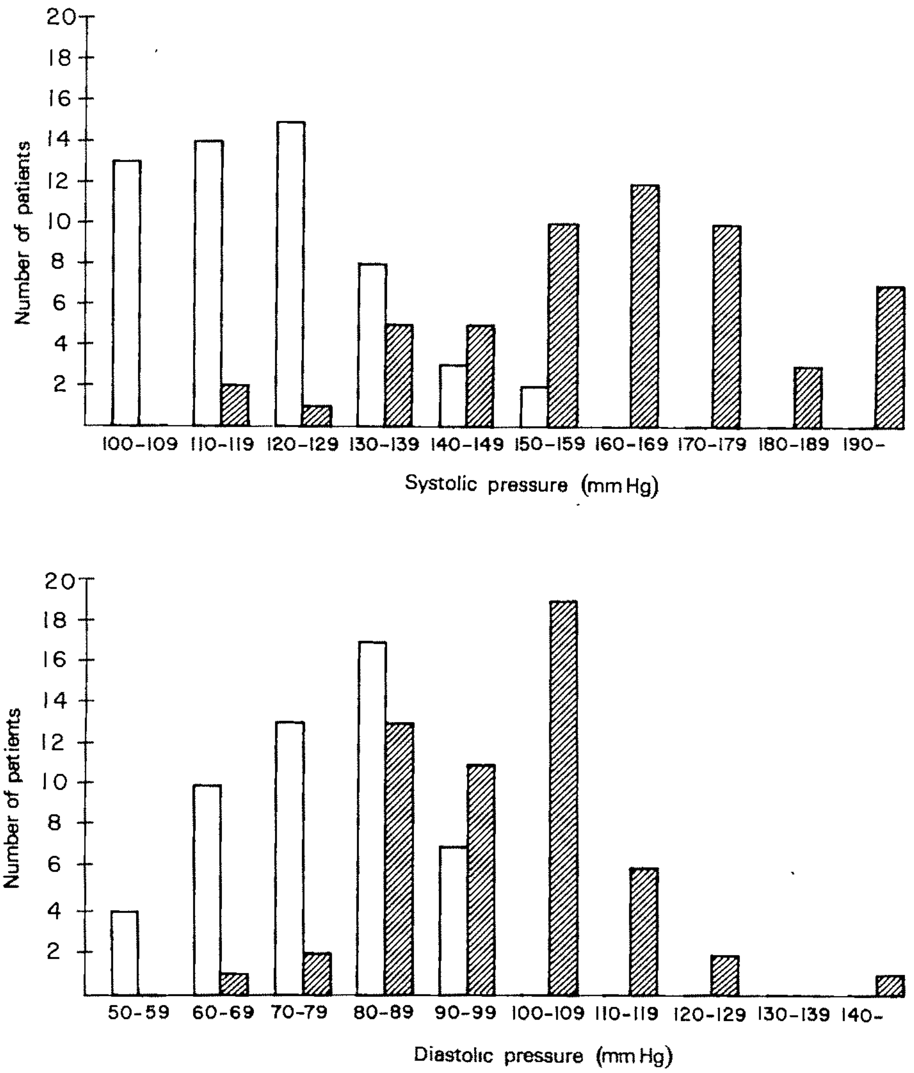

FIG. 1. Distributions of baseline (□) and greatest (▨) arterial pressures of the patients having intraoperative hypertension.

anaesthesia (Cole, 1952). During low spinal block (T10 or lower) while a pneumatic tourniquet has been applied, the patient may complain of a severe dull ache in the leg, even though the cutaneous level of anaesthesia is above the level of the tourniquet. This pain becomes apparent 45–60 min after the tourniquet has been inflated, and is relieved immediately after release of the tourniquet. Although the mechanism of the pain is controversial (Egbert and Deas, 1962; Egbert, 1964; de Jong, 1964) it is thought to be mediated by unmyelinated, slow conducting C-fibres which traverse the sympathetic trunks before entering the spinal cord above the level of block (de Jong and Cullen, 1963). This "slow" pain is normally inhibited by earlier arriving "fast" pain impulses from myelinated A-δ fibres. Limb compression by the tourniquet causes loss of conduction in large nerve fibres before small ones. After about 30 min of tourniquet compression the A-δ fibres are blocked, thus removing inhibition from the still functioning small C-fibres.

The variable efficacy of different anaesthetics in preventing tourniquet hypertension could be explained by their ability to block the C-fibre afferents. A high spinal block should be completely effective. In addition, the ability of different general anaesthetics to abolish cardiovascular reflexes and to produce direct cardiac depression would modify the pressure response to the "slow" pain.

Anaesthetists frequently choose nitrous oxide-narcotic anaesthesia for old or fragile patients. If a patient in whom hypertension would be seriously detrimental is to undergo surgery requiring a tourniquet, then regional block, halothane or possibly enflurane anaesthesia should be considered.

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HYPERTENSION PROVOQUEE PAR UN GARROT

RESUME

On a repris les feuilles d'anesthésie de 600 patients ayant subi un acte chirurgical du membre inférieur pour déterminer la fréquence de l'hypertension artérielle per-opératoire (définie comme une augmentation de 30% de la pression systolique ou diastolique comparée à la première pression mesurée pendant l'intervention après l'incision). La fréquence globale de l'hypertension per-opératoire chez 500 patients auxquels un garrot avait été posé pendant l'acte chirurgical était de 11%. Les risques d'hypertension étaient plus grands si le patient était âgé, avait une cardiomégalie documentée par le cliché thoracique ou l'e.c.g., ou recevait une anesthésie par morphinomimétiques associés au protoxyde d'azote. Une hypertension pré-existante, une augmentation de la créatininémie, une anémie ou un traitement par des antihypertenseurs, des diurétiques ou des steroids ne se sont pas montrés fortement correllés à l'hypertension peropératoire. Un groupe témoin de 100 patients subissant une chirurgie de la hanche sans garrot a objectivé une hypertension dans 1% des cas.

HYPERTENSION DURCH BLUTLEERE

ZUSAMMENFASSUNG

Anästhesiejournale von 600 Patienten mit operativen Eingriffen der unteren Extremitäten wurden überprüft, um die Häufigkeit intraoperativer arterieller Hypertension (beschrieben als 30% iger Anstieg entweder des systolischen oder des diastolischen Blutdrucks, verglichen mit den registrierten ersten Blutdruckwerten nach dem Hautschnitt festzustellen. Die allgemeine Häufigkeit einer Hypertension während der Operation bei 500 Patienten, bei denen eine Blutleere zur Anwendung kam, betrug 11%. Die Wahrscheinlichkeit einer Hypertension erhöhte sich, wenn der Patient älter war, an einer röntgenologisch oder elektrokardiographisch nachgewiesenen Herzvergrosserung litt, oder eine Narkose mit Stickoxydul oder Narkotika erhalten hatte. Eine vorbestehende Hypertension, erhöhtes Serumkreatinin, Anämie oder eine Behandlung mit Antihypertensiva, Diuretika oder Steroiden standen nicht unbedingt im Zusammenhang mit einer intraoperativen Hypertension. Eine Kontrollgruppe von 100 Patienten, die sich einer Hüftoperation unterzogen haten, ohne dass eine Blutleere angewandt wurde, zeigte eine Hypertension von 1%.

HIPERTENSION INDUCIDA POR TORNIQUETE

SUMARIO

Los registros anestéticos de 600 pacientes sometidos a cirujía de los miembros inferiores fueron examinados para determinar la frecuencia de la hipertensión arterial intraoperatoria (definida como un 30% de aumento ya sea de la presión sistólica ya sea de la diastólica comparado con el primer registro de presión después de la incisión). La frecuencia general de hipertensión durante la operación era de un 11% en 500 pacientes a los cuales se aplicó un torniquete durante la cirujía. La probabilidad de hipertensión aumentó si el paciente tenia edad, sufria de un agrandamiento cardiaco visto en la radiografia o e.c.g. o era sometido a una anestesia narcótica y por óxido nitroso. La hipertensión preexistente, la concentración aumentada de creatinina en el suero, la anemia, o el tratamiento por antihipertensivos, diuréticos, o esteroides no fueron fuertemente asociados con la hipertensión intraoperatoria. Un grupo de control de 100 pacientes sometidos a cirujía de la cadera sin administración de un torniquete mostraron una hipertensión en un 1% de los casos.

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RAT FETAL DEVELOPMENT AND MATERNAL EXPOSURE TO TRICHLOROETHYLENE 100 P.P.M.

T. E. J. HEALY, T. R. POOLE AND A. HOPPER

SUMMARY

Thirty-two inbred Wistar rats (study group) were exposed to trichloroethylene 100 p.p.m. in air for 4 h daily from day 8 to day 21 of pregnancy. A control group (31 rats) was exposed to the same experimental conditions but without the addition of trichloroethylene. All the rats were sacrificed on the 21st day of pregnancy and the ovaries, uterus, liver, lungs, heart and the fetuses were examined. There was no evidence of teratogenesis, but a delay in fetal maturation was suggested by reduced fetal weight ($P < 0.05$) and by an increase in bipartite or absent skeletal ossification centres ($P < 0.005$).

All operating theatre staff are exposed to low concentrations of gaseous and volatile agents which include anaesthetic drugs. The first to describe the unpleasantness of working in unventilated theatres was Frederick Hewitt (1893). Although the adverse effects of chronic exposure to anaesthetic agents were described in the early part of the century (Hirsch and Kappus 1929), it was not until a report by Vaisman (1967) that interest developed in examining the reproductive hazard associated with the use of inhalation agents. Unfortunately, many retrospective human studies (Vaisman, 1967; Askrog and Harvold, 1970; Cohen, Weldon Belville and Brown, 1971; Corbett, 1972, 1974; Knill-Jones et al., 1972) did not provide precise information, nor was the evidence substantiated by meaningful control studies. It has been necessary, therefore, to examine the effects of chronic inhalation of anaesthetic agents by conducting experimental studies in animals. The comparative vulnerability of different mammalian species is largely unknown, but the rat is thought to be an appropriate model for these studies (Wigglesworth, 1974).

The intention by the manufacturers to cease production of medical trichloroethylene aroused a chorus of concern from anaesthetists (Atkinson et al., 1979). Trichloroethylene, an unsaturated chlorinated hydrocarbon, has a marked structural similarity to vinyl chloride, a known carcinogen. Furthermore, trichloroethylene is widely used in industrial processes as a degreasing or as a cleansing agent. It would therefore be informative to examine, in an animal model, the effect of chronic inhalation of a trace concentration of trichloroethylene during pregnancy.

METHOD

Inbred Wistar rats, identified by ear tags, were housed in a breeding room in isolation from other animals. They were fed a standard small-animal diet (Spillers Lab Animal No. 1 Diet): water was freely available except during the exposure periods.

Two nulliparous female rats (body weight 200–300 g) were placed in breeding cages overnight with one proven male. The date of pregnancy was identified by the presence of a vaginal plug or spermatozoa in the vagina. The study and control female rats were housed together. The ambient temperature and relative humidity of the rooms were maintained at 20–32 °C and 70% respectively. Equal numbers of pregnant females were simultaneously exposed to trichloroethylene 100 p.p.m. ($535\,\mathrm{mg\,m^{-3}}$) in room air or to room air in separate stainless steel exposure chambers for 4 h daily from day 8 to day 21 of pregnancy. The selection of rats for exposure to either air or trichloroethylene in air was made using random numbers. The exposures were made simultaneously and the air flow was provided using a single air compressor pump.

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During exposure the concentration of trichloroethylene in the study chamber, and oxygen and carbon dioxide in the control chamber, were measured continuously using an infra-red analyser (Miran) and a Mass Spectrometer (British Oxygen) respectively. During the pregnancy, rats were weighed daily and the daily food and water consumption was recorded.

To avoid the effect of diurnal variation (Basford and Fink, 1968) all rats were exposed in the chambers at the same time of the day. All female rats were sacrificed on the 21st day of pregnancy. The abdominal viscera were exposed and the ovaries, uterus, liver, lungs and heart were carefully examined using the dissecting microscope. The number of corpora lutea of pregnancy were counted. The uterus was opened to determine the number of fetuses present and also the number and position of the placental sites.

All fetuses were weighed, sexed (ano–genital distance) and measured (crown–rump length). Each fetus was examined to identify any external malformations. The body cavity was opened by a mid-ventral incision and the following organs were removed and examined: lungs, diaphragm, liver, gastrointestinal system, heart and kidneys. Care was taken to avoid damage to the skeletal system. Fetuses were preserved in 95% ethanol for alizarin red-S staining and skeletal examination.

Trichloroethylene used in this study was distilled from Trilene (ICI).

An unpaired *t* test (weighted for litter size) was used to compare the control and study values for fetal weight and fetal length, and a Chi square analysis for the number of rats in which total resorption occurred. The comparisons by fetal count (number of resorptions, litter size, sex and skeletal abnormalities) were made using the Mann–Whitney *U* test (Siegal, 1956).

RESULTS

Initially, 71 female rats were studied. Two of the rats allocated to the study group died, one on day 13 and the other on day 8 of pregnancy. Both the rats were pregnant, but the fetuses were too small for examination and therefore none of the data collected was included in the present study. The two rats died because of an obstruction in the air supply system leading to a trichloroethylene overdose. No other rats were in the study chamber on that occasion. Three rats in each group showed corpora lutea of normal cycle and therefore had not been pregnant or had resorbed very early in pregnancy. Results obtained from these rats were not included in the study.

The effect of chronic inhalation of trichloroethylene 100 p.p.m. by the pregnant rat during day 8 to 21 is shown in table I. There was a total of 423 fetuses (31 control dams with 236 fetuses; 32 dams with 187 fetuses). The frequency of fetal loss (fetal death and resorption per litter) was not significantly greater in the group exposed to trichloroethylene ($P = 0.054$), nor was the litter size altered ($P = 0.061$). The frequency of fetal loss in early pregnancy (the difference between the number of corpora lutea and the sum of the visible fetuses and placental sites) was not significantly greater in the group exposed to trichloroethylene ($P = 0.26$). However, the number of rats in which total resorption of all fetuses occurred was greater in the study group ($P < 0.05$). Fetal weight was reduced ($P < 0.05$), but crown–rump length was

TABLE I. *Effect of maternal rat exposure to trichloroethylene 535 mg m^{-3} on fetal development *Mann–Whitney* U *test; **unpaired* t *test; ***Chi-square test. c–r = crown–rump length*

	Maternal rat			Fetal rat							
Group	No. rats	No. with fetus	Litters with total resorption	Litter size	No. early resorptions per litter	No. resorptions per litter	Total no. fetuses	Fetal wt. (g)	Fetal c-r (cm)	Fetal sex	Skeletal anomalies
Control	31	29	2	8.14 ±0.34	1.233 ±0.218	1.72 ±0.06	236	3.21 ±0.03	3.32 ±0.01	1.03 : 1 M : F	70% normal
Study	32	25	7	7.48 ±0.23	2.50 ±0.533	2.44 ±0.08	187	2.93 ±0.04	3.21 ±0.021	0.83 : 1.0 M : F	50% normal
P			<0.05***	0.0607*	0.262*	0.0537*		<0.05	<0.1	0.065*	0.0026*

not significantly altered ($P<0.1$). There was an apparent reduction in the ratio of male to female fetuses, but this was not statistically significant ($P = 0.065$). No external visceral or gross skeletal anomalies were found in either the control or the study fetuses. Abnormalities of the sternum, which included complete absence of sternal ossification centres and bipartite patterns, occurred in both groups. No supplementary ribs were noted. The frequency of minor variations (absent or bipartite centres of ossification) was greater in the study group ($P = 0.003$).

DISCUSSION

In this study chronic inhalation of trichloroethylene 100 p.p.m. from day 8 to 21 of pregnancy has been shown to result in reduced fetal weight, which suggests that trichloroethylene retards fetal development. This conclusion is supported by the increased frequency of bipartite or absent ossification centres in the study group (Fritz and Hess, 1970). Inhalation of trichloroethylene was not associated with a significantly increased fetal loss. Fetal loss was identified by comparing the numbers of live fetuses with the total number of corpora lutea present. Fetal loss during the early part of the pregnancy was calculated by deducting the number of placental sites from the number of corpora lutea of pregnancy. Although the difference between the groups, in terms of early resorption, was not significantly different, there was a difference between the control and study groups in terms of total resorption of all fetuses. This suggests that trichloroethylene may be toxic to the Wistar fetus in the early stages of pregnancy.

On the other hand, Schwetz, Leong and Gehring (1975) exposed pregnant rats and mice to trichloroethylene 300 p.p.m. for 7 h per day on days 6–15 of pregnancy, and reported that there was no evidence of embryotoxicity or teratogenicity. However, in another study Kimmerle and Eben (1973) have suggested that the pharmacokinetic behaviour of trichloroethylene following acute exposure is different from that following repeated exposure. A short-term exposure might lead, therefore, to an underestimation of the embyrotoxicity or teratogenicity of trichloroethylene. It is during the period of organogenesis that the fetus is most susceptible to a teratogenic insult. The present study seems particularly relevant in that the pregnant rats were exposed to trichloroethylene during an extended period, day 8 to day 21, which included the period of rapid organogenesis.

The comparative vulnerability of different animal species to fetotoxic substances is largely unknown, but it has been suggested (Wigglesworth, 1974) that the rat is a suitable model for this type of study and that results obtained may be comparable with results to be expected in human studies. Nonetheless, the comparisons must be made with caution: the metabolic behaviour of trichloroethylene may be species dependent. When rats are exposed to comparable concentrations of trichloroethylene, chloral hydrate is produced, but this is not detected after human exposure (Kimmerle and Eben, 1973).

It is well recognized that minor stress induced by environmental changes, which include handling, may lead to resorption of the fetus in rats. In the present study, therefore, environmental changes and handling were reduced to the minimum commensurate with the recording of physical data and exposure in the chamber. Furthermore, the rats in the study and control groups were exposed to the same stimuli and at the same time of day so that the influence of stress and diurnal variation (Basford and Fink, 1968) was excluded or was the same for both groups.

The retardation in fetal development associated with chronic inhalation of a trace concentration of trichloroethylene reported here supports the findings of Dorfmueller and others (1979) who reported evidence of delay in maturation rather than teratogenesis when female rats were exposed to trichloroethylene 1800 ± 299 p.p.m. during 20 days of pregnancy, and finds a parallel in the findings of Viera (1979) who exposed pregnant rats to nitrous oxide 5000 p.p.m. in air. On the other hand, the consensus is that halothane in trace concentrations, alone or in combination with nitrous oxide, has no similar effect (Bruce, 1973: Lansdown et al., 1976: Pope et al., 1978: Coate, Knapp and Lewis, 1979). Indeed Wharton and others (1978) concluded that, to demonstrate fetotoxicity, halothane concentrations 40 times greater than those found in unscavenged operating theatres were needed. Comparison between the results obtained by human studies is impossible, but fetotoxicity as a result of inhalation of trace concentrations in the human cannot be excluded. The results presented here do not suggest that trichloroethylene has teratogenic properties in trace concentrations although there is a hint that it may be fetotoxic in the earliest stages of pregnancy. Although the probabilities shown in table I are, in some cases, just short of the commonly accepted level at which the null hypothesis is firmly rejected, this paper is concerned with a safety factor and it may therefore be valid to increase the significance level of the null hypothesis from 5% to 10%.

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DEVELOPPEMENT DU FOETUS DE RAT APRES EXPOSITION DE LA MERE AU TRICHLORO-ETHYLENE 100 P.P.M.

RESUME

Trente-deux rates de race Wistar (groupe d'étude) ont été exposées au trichloro-éthylène 100 p.p.m. dans l'air 4 h par jour, du 8e au 21e jour de leur grossesse. Un groupe témoin (31 rates) ont été mises dans les mêmes conditions expérimentales mais sans adjonction de trichloroéthylène. Toutes les rates ont été sacrifiées au 21e jour de la grossesse et on a examiné les ovaires, l'utérus, le foie, les poumons, le coeur et les foetus. On n'a pas retrouvé d'argument en faveur d'une tératogènese mais l'existence d'une diminution de poids du foetus ($P < 0,05$) et d'une augmentation du dédoublement voire d'une absence des points d'ossification squelettiques ($P < 0,005$) suggèrent un retard dans la maturation foetale.

DIE ENTWICKLUNG DES RATTENFOETUS UND EXPOSITION DER MUTTERTIERE MIT TRICHLORÄTHYLEN 100 p.p.m.

ZUSAMMENFASSUNG

Zwei und dreissig Inzucht-Wistar-Ratten (Studiengruppe) wurden 4 Stunden täglich vom 8. bis zum 21. Tag der Schwangerschaft Trichloräthylen 100 p.p.m. in Luft ausgesetzt. Die Kontrollgruppe (31 Ratten) wurde den gleichen Bedingungen unterworfen, jedoch ohne Trichloräthylen. Alle Ratten wurden am 21. Tag der Schwangerschaft getötet und Eierstöcke, Gebärmutter, Leber, Lungen, Herz und Foetus untersucht. Es gab keine Zeichen einer Teratogenese, jedoch wurde aufgrund des reduzierten Gewichts der Foeten ($P < 0,05$) und aufgrund der Zunahme von gespaltener oder fehlender Knochenbildung des Skeletts eine Wachstumsverzögerung der Foeten angenommen.

DESARROLLO FETAL EN LAS RATAS Y EXPOSICION MATERNAL AL TRICLOROETILENO EN UNA CONCENTRACION DE 100 P.P.M.

SUMARIO

Treinta y dos ratas Wistar cosanguíneas (grupo de estudio) se expusieron al tricloroetileno en una concentración de 100 p.p.m. en el aire por espacio de 4 horas diarias, desde el octavo hasta el veintiunavo día del embarazo. Un grupo de control (31 ratas) se expuso a las mismas condiciones experimentales pero sin la adición del tricloroetileno. Todas las ratas se sacrificaron al cumplirse el 21 día del embarazo, examinándose los ovarios, el útero, el hígado, los pulmones, el corazón y el feto de todas ellas. No hubo evidencia alguna de teratogénesis, pero hubo indicios de un retraso en la maduración fetal a causa de la reducción del peso de los fetos ($P<0{,}05$) y de un incremento, o ausencia, de los centros de osificacion del esqueleto ($P<0{,}005$).

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ANTICONVULSANT ACTIVITY OF ALTHESIN ON EXPERIMENTAL EPILEPSY

P. L. De Riu, G. Susini and P. Ruju

SUMMARY

Anaesthetic doses of Althesin were tested in rabbits using two experimental models of epilepsy: generalized (OHP; oxygen at high pressure-induced seizure) and partial (penicillin cortical-induced seizure). Althesin in both models always produced anticonvulsant activity which was more powerful in generalized convulsions. This agent was successful in preventing and treating OHP seizures. The authors conclude that a clinical history of convulsions must not be considered a contraindication to the use of this anaesthetic which has particularly useful properties for neurosurgery.

Convulsions during steroid anaesthesia were reported by Selye (1941) who described occasional fits when he injected steroids i.p. to rats. The steroid anaesthetic agents used before Althesin were hydroxydione and GR2/146. The convulsant properties of hydroxydione were first described by Price (1962), but none were reported following GR2/146. In 1973, Uppington reported convulsions following Althesin and another case was described by Rees (1975).

It was suggested that Althesin has an action similar to hydroxydione and in epileptics may cause a pre-existing resting focus to discharge and thereby produce seizures (Uppington, 1973). It was also suggested that Althesin could be considered useful to activate e.e.g. patterns in epileptics (Testa, Comelli and Saia, 1977). The appearance of paroxysmal bitemporal abnormalities in e.e.g. traces of epileptic subjects during Althesin anaesthesia was also observed (Sramka, 1975). However, Bimar and Lepouleuf (1973) reported that Althesin greatly increases the cardiazolic threshold in cats, and Emperaire and Bimar (1973) stressed that, in small doses, this drug has a consistent anticonvulsant effect on photic epilepsy in baboons. Recently, two cases of status epilepticus which did not respond to classic drugs such as diazepam and clonazepam, were successfully treated with Althesin by Alati and others (1979). According to these authors, burst suppression could be a major factor in the anticonvulsant action of Althesin since it could break the circle of epileptic discharge leading to increased oxygen consumption.

Munari and others (1977) showed that seven other cases of status epilepticus resistent to benzodiazepines were successfully treated with an anaesthetic dose of Althesin. Therefore we administered Althesin to two models of experimental epilepsy, focal and generalized in different experimental conditions to determine whether it had any convulsant or anticonvulsant action.

MATERIALS AND METHODS

Twenty adult rabbits of either sex weighing 2–3 kg were allocated to two main groups: in the first, 10 animals were exposed to oxygen at high pressure (OHP) to obtain a generalized centrencephalic seizure, while in the second group, 10 animals underwent cortical focal convulsion using penicillin.

Group 1

The animals were anaesthetized with ether and two pairs of stainless steel electrodes aseptically implanted in the skull for e.e.g. recording (Fp1-Fp2, 01-02). Twenty-four hours afterwards, the right cephalic vein was cannulated with a Teflon catheter under local anaesthesia (2% lignocaine 2 ml) and 3 h later the animals were exposed to OHP in a 15-litre hyperbaric chamber which had a device for injecting a drug to the cephalic catheter of the animals. The chamber was flushed with 100% oxygen for 2 min, the outlet valve sealed and the pressure increased at a uniform rate over 2 min until a pressure of 6 atm was reached.

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After 17–21 min of continuous exposure at 6 atm, the e.e.g. patterns gradually changed with a marked reduction in frequency and increase in amplitude of the waves. This is considered a preseizure activity which occurs when a convulsive seizure is imminent (Raday et al., 1975). At the exact moment when preseizure activity occurred, Althesin was injected i.v. in a single dose of 0.1 ml kg^{-1}. The total exposure at 6 atm was 60 min. Five rabbits were treated in this way. Five other rabbits had an Althesin injection of the same dose at the onset of the first paroxysmal discharge after 20–23 min of continuous OHP exposure at 6 atm. The total exposure time in this subgroup was also 60 min. In all cases, decompression was carried out over 5 min.

Group 2

The animals were anaesthetized with ether and one pair of stainless steel screw electrodes implanted in the frontal region (Fp1–Fp2). The next day 1 cm^2 on the left temporo–parietal region was exposed through a trephine hole under halothane anaesthesia and the dura was opened. E.e.g. was recorded by the screw electrodes previously attached to the skull while the electrocorticogram (e.co.g) was recorded from silver ball electrodes applied to the pia. Convulsions were produced by applying a small pledget soaked with sodium penicillin G 40 000 u. ml^{-1} to the pia. The first spike in the cortical focus appeared 100–120 s after penicillin was applied. When the spikes reached an amplitude of more than 250 µV, Althesin was injected i.v. in a single dose of 0.1 ml kg^{-1} to five rabbits. In the remaining five rabbits, Althesin was injected in the same dose about 20 min after the penicillin application, when the highest spike frequency was reached in the cortical focus. In all experiments, the time of injection of the Althesin was 5 s. At the end of each experiment, the animals were sacrificed with a lethal dose of pentobarbitone.

RESULTS

In the first five animals of group 1, Althesin was injected when the preseizure e.e.g. patterns appeared (fig. 1B); in four cases it prevented seizures despite continued exposure to OHP. In one rabbit, an electrical seizure appeared after 46 min of exposure, although the animal showed no clinical symptoms.

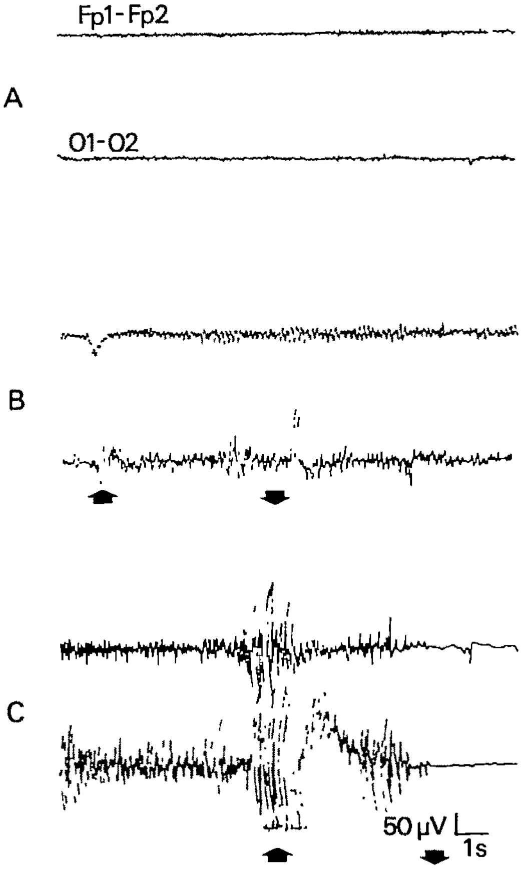

FIG. 1. A: Normal patterns recorded from frontal and occipital areas. B: Preseizure activity characterized by decrease of frequency and increase in voltage of waves which become peaked. Time of injection 5 s. C: Onset of first epileptic hyperoxic discharge which is shown by appearance of high voltage burst of hypersynchronous spikes. Before the end of injection, paroxysmal electrical activity has completely disappeared. Time of injection 5 s. Arrows denote start and finish of Althesin injection.

In the second subgroup of rabbits in group 1, Althesin was injected immediately after seizure began and in all cases stopped clinical and electrical paroxysmal signs immediately after administration (fig. 1C). Exposure at 6 atm also lasted 1 h in the second subgroup, but after Althesin, none of the OHP-exposed rabbits had convulsions or abnormal electrical activity. None of the animals showed seizure activity during the decompression period.

In the second group, Althesin was injected when the isolated spikes reached greatest amplitude. Spikes (fig. 2B) and clonic jerks of the right forelimb were stopped in all cases for at least

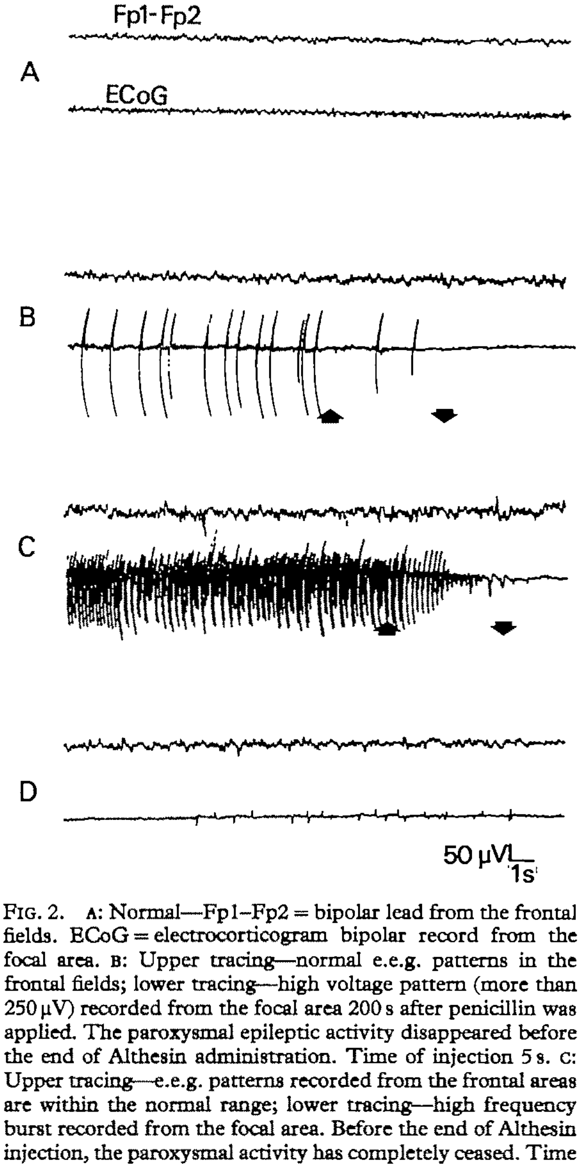

FIG. 2. A: Normal—Fp1–Fp2 = bipolar lead from the frontal fields. ECoG = electrocorticogram bipolar record from the focal area. B: Upper tracing—normal e.e.g. patterns in the frontal fields; lower tracing—high voltage pattern (more than 250 μV) recorded from the focal area 200 s after penicillin was applied. The paroxysmal epileptic activity disappeared before the end of Althesin administration. Time of injection 5 s. C: Upper tracing—e.e.g. patterns recorded from the frontal areas are within the normal range; lower tracing—high frequency burst recorded from the focal area. Before the end of Althesin injection, the paroxysmal activity has completely ceased. Time of injection 5 s. D: 6 min after C. Upper tracing—normal electrical activity; lower tracing—isolated spikes begin to appear again in the focal area. Arrows denote start and finish of Althesin injection.

6 min. In rabbits which received Althesin when the spikes reached the highest frequency, the paroxysmal epileptical activity was abolished in all cases before the end of the administration (fig. 2C). Isolated spikes appeared again following an electric silence lasting about 5 min (fig. 2D) and in a short time reached large amplitude, but high frequency bursts did not reappear.

DISCUSSION

Seizures induced by hyperbaric oxygen appear to provide a suitable model for the study of epilepsy (Wood, 1972). There are similarities between OHP-induced seizures and human epilepsy:
(i) e.e.g. patterns and signs of the two types of seizures are similar (Rucci, Giretti and La Rocca, 1967; Wood, 1972; Hanna et al., 1978);
(ii) derangement of cerebral gamma amino butyric acid (GABA) metabolism occurs in OHP-induced seizures as well as in some stages of epilepsy (Wood, 1972).

Furthermore, impairment of cerebral GABA metabolism also seems to be involved in focal convulsions produced by local application of cobalt and penicillin (Mutani et al., 1977).

It would appear that a similar biochemical mechanism is involved in experimental and human epilepsy and OHP may serve as a model to evaluate potential antiepileptic agents the mode of action of which does not depend on antioxidant properties (Wood, 1972).

Our results show that Althesin protects animals exposed to OHP against seizures and also stops hyperoxic convulsions when injected at the onset of the first paroxysmal discharge. Althesin produced a rapid and prolonged anticonvulsant effect in this form of seizures. This may be explained by the following:
(a) The primary event in OHP convulsions is probably major neuronal oxidation (Wood, 1972) with reduction of brain GABA concentration a secondary event (Wood, 1972). Althesin reduces cerebral oxygen consumption by about 46% (Sari et al., 1976) and may act prophylactically by reducing oxidation.
(b) Vasoconstriction in OHP may protect against neuronal oxidation (Deutrebond and Haldane, 1921). Since Althesin produces cerebral vasoconstriction demonstrated by angiography (Laxenaire, 1975), this may augment the vasoconstrictor effect of OHP.
(c) Althesin has a greater depressant effect on the reticular activating system (RAS) than the cerebral cortex (Bimar and Lepouleuf, 1973). The first discharge occurs in the RAS for all types of generalized convulsions (Gastout and Fischer, 1959; Rolston and Langer, 1965) including hyperoxic convulsion (Rucci, Giretti and La Rocca, 1967) and may be prevented by Althesin.

These three factors could explain the particular efficacy of Althesin on hyperoxic seizures.

Althesin also showed an anticonvulsant action during focal convulsions. Its activity in this experimental model is constant but of short duration and is probably related to the depressant cortical action. Moreover, it produces prolonged suppression of high frequency bursts which are signs of increased cortical excitability. This suggests that Althesin in an anaesthetic dose has a depressant effect on the cerebral cortex which is mild but more prolonged than expected.

In conclusion, Althesin seems to have a powerful anticonvulsant action when tested on a model of generalized convulsion and on a model of focal convulsion. Our findings are in agreement with the report that this steroid agent has a depressant activity upon the reticular activating system and cerebral cortex and first description of the anticonvulsant properties of this agent on cardiazolic convulsions in cats (Bimar and Lepouleuf, 1973) and photic seizures in baboons (Emperaire and Bimar, 1973). Our data also support reports that Althesin was effective in treating status epilepticus (Munari et al., 1977; Alati et al., 1979) and suggest that a clinical history of convulsions must not be considered a contraindication to Althesin. Althesin also reduces intracranial pressure and brain oxygen consumption (Sari et al., 1976) and should be a useful anaesthetic for neurosurgery where partial or generalized seizures are common. The two examples of generalized convulsion following Althesin injection (Uppington, 1973; Rees, 1975) cannot be explained by the results of our study, but the suggestion that Althesin can cause a silent epileptic focus to discharge seems unlikely.

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ACTIVITE ANTICONVULSIVANTE DE L'ALFATESINE DANS L'EPILEPSIE EXPERIMENTALE

RESUME

On a étudié des doses anesthésiques d'alfatésine chez des lapins, en utilisant deux modèles expérimentaux d'épilepsie: épilepsie généralisée (crise induite par l'OHB = oxygène hyperbare) et localisée (crise provoquée par de la pénicilline sur le cortex). Dans les deux modèles expérimentaux, l'alfatésine a toujours objectivé une activité anticonvulsivante, plus puissante au cours des crises généralisées. Cet agent a permis de prévenir et de traiter les crises dues à l'OHB. Les auteurs concluent que des antécédents cliniques de convulsions ne doivent pas être considérés comme une contre-indication à l'usage de cet anesthésique qui a des propriétes particulièrement utiles en neurochirurgie.

ANTIKONVULSIVE AKTIVITÄT VON ALTHESIN AUF EXPERIMENTELLE EPILEPSIE

ZUSAMMENFASSUNG

Anästhetisch wirksame Dosen von Althesin wurden bie Kaninchen getestet, und zwar experimentell an zwei Formen einer Epilepsie: die generalisierte, aufgrund eines auf Sauerstoffhochdruck zurückzuführenden Krampfes, un die partielle, durch Penicillin cortikal-induzierte Krämpfe. Althesin zeigte in beiden experimentellen Modellen immer eine antikonvulsive Aktivität, die jedoch bei den generalisierten Krämpfen stärker ausgeprägt war. Die Substanz lieferte besonders gute Ergebnisse bei der Verhütung und Behandlung eines auf Sauerstoffhochdruck zurückzuführenden Anfalles. Die Autoren schliessen daraus, dass eine Anfallsanamnese nicht als Kontraindikation für die Anwendung dieses Anästhetikums angesehen werden sollte, da es durchaus positive Eigenschaften für den Gebrauch in der neurochirurgie besitzt.

ACTIVIDAD ANTICONVULSIVA DE LA ALTESINA EN EPILEPSIA EXPERIMENTAL

SUMARIO

Se llevaron a cabo ensayos sobre dosis anestèticas de Altesina en conejos usándos dos modelos experimentales de epilepsia: generalizada (OHP; oxígeno en crisis inducida por presión alta) y parcial (crisis inducida corticalmente por penicilina). En ambos modelos, la Altesina siempre produjo una actividad anticonvulsiva que se reveló más potente en las convulsiones generalizadas. Este agente fue exitoso en el tratamiento y la prevención de las crisis OHP. Los autores concluyen que un historial clínico de convulsiones no debe considerarse como una contraindicación del uso de dicho anestético que posee propiedades particularmente útiles en la neurocirujia.

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HALOTHANE HEPATITIS IN A YOUNG CHILD

R. B. LEWIS AND M. BLAIR

SUMMARY

A 4-year-old girl developed severe hepatitis following the fourth administration of halothane in a period of 5 months. She was shown to have a circulating antibody which acted specifically against rabbit hepatocytes previously sensitized to halothane. The patient made a full recovery from the hepatitis, but 5 months later, developed diabetes mellitus.

Halothane is metabolized in humans via at least two pathways, oxidation and reduction, and both have been shown in experiments to be associated with the production of chemically reactive metabolites. McLain, Sipes and Brown (1979) have demonstrated in animals that halothane may be directly toxic to the liver where there is stimulation of the reductive pathway, whereas Davis and colleagues (1980) have evidence that the antigen of the halothane-altered membrane is produced only when the oxidative pathway is activated.

In a *British Medical Journal* Editorial on The Liver and Halothane—Again (Editorial, 1980) it was suggested that a reasonable sequence of causation was: halothane with special factors (hypoxia and enzyme induction) causing enhanced metabolism to produce reactive metabolites with binding to intracellular elements, consequent cell damage, release of transaminases and hepatic cellular necrosis. The important practical lesson from this work is that it draws attention to a group of patients in whom the use of halothane a second time would be theoretically more hazardous. These include patients who are fat, elderly, likely to have enzyme induction, are being stressed with other reactive metabolites (during radiotherapy for example), are undergoing an operation or anaesthetic technique with an appreciable effect on liver blood flow, have an incision or postoperative complication predisposing to hypoxia, and are likely to be still metabolizing a dose of halothane given within the previous 2 weeks. Care in avoiding repeat halothane anaesthetics in these circumstances would probably reduce the already small frequency of this complication even further. According to Davis and others (1980) mild hepatic damage, seen in up to 20% of patients repeatedly anaesthetized with halothane, may be a manifestation of direct toxic injury. If the extremely rare, more severe lesion develops, an additional immune component may be involved.

The actual demonstration of a circulating antibody, in patients with hepatitis, to halothane-altered hepatocytes is credited to Vergani, Mieli–Vergani and co-workers (1978). Because many of the clinical features of halothane hepatitis suggest an immune-mediated pathogenesis, they studied patients with this condition in a search for circulating antibodies directed against halothane-altered hepatocyte membrane components.

Reports of post-halothane hepatitis in children are extremely rare. In a review of 203 patients with postoperative jaundice (Walton et al., 1976), two children aged 4 and 5 yr were originally included in the series, but a panel of hepatologists were not unanimous about the findings and they were later excluded.

CASE REPORT

A three-year-old girl presented with a history of recurrent urinary tract infections. She was found to have a duplex left kidney with a ureterocele associated with the ureter draining the upper pole which also showed changes suggesting chronic pyelonephritis. Over the next 5 months, she had four general anaesthetics for surgical procedures (two major procedures and two cystoscopic examinations), during which she received halothane (table I).

For the two cystoscopic examinations pethidine 1.5 mg kg^{-1} and atropine 0.6 mg premedication

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TABLE I. *The patient's anaesthetic record—four procedures*

	1st cystoscopy	Left heminephrectomy and ureterectomy	2nd cystoscopy	Excision of left ureterocele + reimplantation left ureter
Date	27.4.77	1.6.77	31.8.77	28.9.77
Weight	18 kg	18.2 kg	20 kg	18 kg
Premedication	Atropine 0.6 mg Pethidine 35 mg	Atropine 0.6 mg Morphine 2 mg	Atropine 0.6 mg Pethidine 30 mg	Atropine 0.6 mg Pethidine 25 mg
Anaesthetic Induction	Inhalation Nitrous oxide, oxygen +2% halothane	Inhalation Nitrous oxide, oxygen +2% halothane	Inhalation Nitrous oxide, oxygen +2% halothane	Inhalation Nitrous oxide, oxygen +2% halothane
Maintenance	Nitrous oxide, oxygen +0.5% halothane	Tubocurarine 10 mg. Intubation (Howells Ventilator), IPPV with nitrous oxide, oxygen+0.5% halothane. Atropine 0.4 mg+ neostigmine 1.5 mg→ spontaneous ventilation	Nitrous oxide, oxygen +1.5% halothane	Tubocurarine 10 mg. Intubation (Sheffield Ventilator), IPPV with nitrous oxide, oxygen+0.5% halothane. Atropine 0.4 mg+ neostigmine 1.5 mg→ spontaneous ventilation
Duration	10 min	3 h	10 min	1 h 30 min
I.v. fluids				
Intraoperative electrolytes	Nil	Ringer Lactate 300 ml	None	Ringer Lactate 400 ml
Intraoperative blood	Nil	None	None	None
Postoperative	Nil	5% Dextrose 500 ml (8 h) Ringer Lactate 500 ml (8 h) 5% Dextrose 500 ml (8 h) Ringer Lactate 500 ml (8 h)	Nil	5% Dextrose 500 ml (8 h) Ringer Lactate 500 ml (8 h) 5% Dextrose 500 ml (8 h) Repeated for 24 h
Postoperative analgesia	Nil	Morphine 2 mg 6-hourly for 48 h—given thrice	Nil	Pethidine 25 mg 6-hourly for 48 h. PRN-given 6-hourly
Postoperative complications	Nil	Increase of temperature for 24 h—(38 °C) 72 h after operation	Nil	Jaundice at 48 h

were given i.m. 45 min before operation. On both occasions an inhalation technique was used—66% nitrous oxide in oxygen supplemented with halothane up to 2%.

For the major procedures premedication comprised atropine 0.6 mg with morphine 2 mg (0.1 mg kg^{-1}) for the left heminephrectomy and ureterectomy, and pethidine 25 mg (1.5 mg kg^{-1}) for the excision of the ureterocele and reimplantation of the left ureter. Premedication was given 45 min before operation. The anaesthetic technique consisted of inhalation induction with 66% nitrous oxide in oxygen supplemented with halothane sufficient to allow tracheal intubation. Neuromuscular blockade was produced with tubocurarine 10 mg.

Ventilation of the lungs was controlled using the same gas mixture supplemented with 0.5% halothane delivered from a Howells Ventilator.

Antagonism of neuromuscular blockade at the end of the procedures was with neostigmine 0.06 mg kg^{-1} preceded by atropine 0.02 mg kg^{-1}.

Forty-eight hours after the final operation the patient became jaundiced. The greatest value of serum bilirubin was 372 μmol litre^{-1} on the 19th day after operation. The jaundice was hepatocellular in origin, the serum transaminases being dramatically increased (AST 3755 iu litre^{-1}, ALT 1438 iu litre^{-1}) on the 2nd day after operation. There was hypoprothrombinaemia and a leucocytosis. Full biochemical and haematological data are presented in table II. Figure 1 shows the effect of the hepatocellular damage on the serum bilirubin and alanine aminotransferase (ALT) related to time. At no time during any procedure was there clinical evidence of hypovolaemia, hypotension or hypoxia. The patient did not receive any blood or blood products and tests for hepatitis B antigen were negative. Other virological tests did not yield evidence of recent infection and in particular there was no evidence of hepatitis A antibody. The clinical and biochemical course was not typical of infective hepatitis, the commonest cause of jaundice in childhood.

The patient remained jaundiced for 6 weeks, but improved steadily in that time although, on the

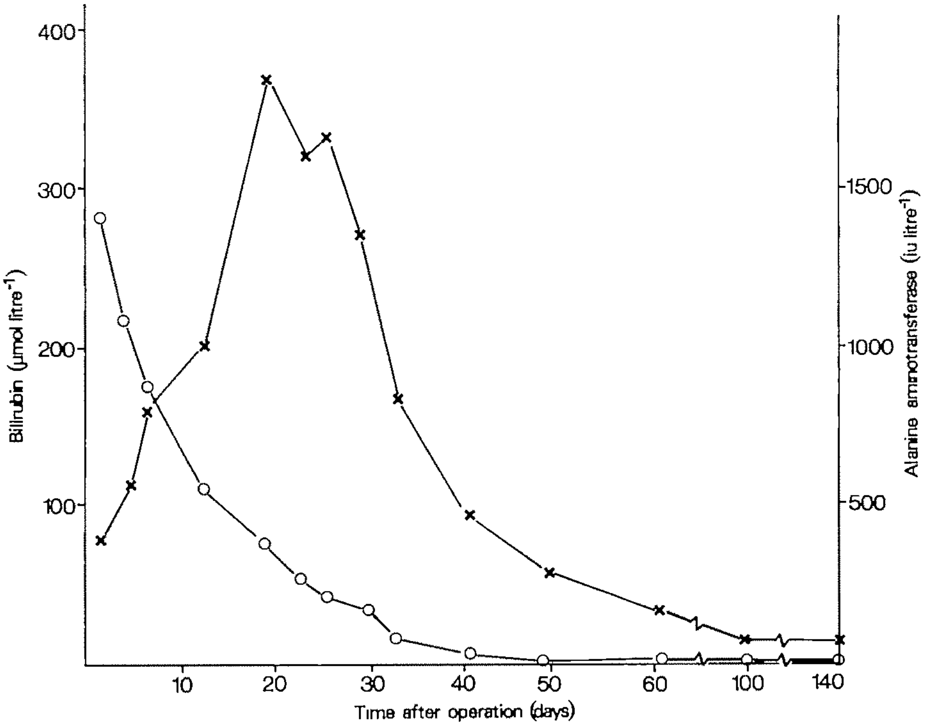

FIG. 1. Effect of hepatocellular damage on serum bilirubin (x——x) and alanine aminotransferase (O——O) related to time after operation (days).

TABLE II. *Summary of liver function tests and haematological results following fourth administration of halothane*

	Time scale (days before and after operation)																
	−2	0	+1	+2	+5	+7	+12	+19	+23	+26	+29	+33	+41	+48	+62	+104	+144
Bilirubin (μmol litre^{-1})				80	114	160	200	372	321	336	270	166	92	54	34	15	10
Direct				+	+	+	+	+	+	156	160	+	+	+	+		
Alkaline phosphatase (iu litre^{-1})				182	192	192	162	196	208	212	218	180	150	146	190		238
Total protein (g litre^{-1})				54	58	60	57	59	60	68	64	57	66	70	71	68	66
Albumin (g litre^{-1})				32	31	27	27	28	30	33	31	30	37	37	40	39	45
Globulin (g litre^{-1})				22	27	33	30	31	30	35	33	27	29	33	31	29	21
AST (iu litre^{-1})				3755	958	1065	846	868	528	479	272	158	79	71	81	50	19
ALT (iu litre^{-1})				1438	1087	883	549	389	268	245	168	88	51	33	48	35	16
Hb (g dl^{-1})	14.6		11.7	11.6	13.1	11.6	10.6	10.7	10.6		10.9	9.9	10.9	9.9	11.0		
WBC × 10^9 per litre	11.1		17.1	14.0	20.0	21.5	21.1	17.5	12.3		13.8	12.3	13.0	6.2	10.5		
Differential count																	
Neutrophils			76%			64%	64%	70%	65%		17%	58%	47%				
Lymphocytes			18%			26%	34%	24%	28%		73%	40%	48%				
Monocytes			4%			10%	2%	6%	6%		10%	2%	4%				
Eosinophils			2%						1%				1%				
Platelets × 10^9 per litre	497		515	418	392	650	669	534	468		483	349	476	364	462		
Urea and electrolytes	Normal values throughout																
Prothrombin index					54%		54%	57%	67%			92%					

20th day after operation, there was sudden onset of ascites and generalized oedema which cleared with the use of diuretics and spironolactone.

The patient was discharged from hospital on the 35th day after operation with minimal jaundice and was progressing satisfactorily for a time. Five months after her final operation, she was readmitted in diabetic ketoacidosis. At present her blood sugar is controlled with daily insulin and her hepatic and renal functions are satisfactory.

DISCUSSION

This patient developed severe hepatocellular jaundice shortly after the fourth administration of halothane. During the convalescent phase of the illness, the patient's blood was shown to contain an antibody directed specifically against prepared rabbit hepatocytes which had previously been exposed to halothane. This antibody has been found in conjunction with severe halothane-associated hepatitis and does not occur after halothane exposure without liver damage (Vergani, Tsantoulas et al., 1978). The repeated exposure to halothane at intervals of 4–8 weeks appears to have initiated an antibody response to hepatocytes sensitized to halothane or one of its metabolites.

It could be argued that the exposure of this child to halothane four times in 5 months constitutes clinical imprudence, but if one studies the literature there is very little evidence that such exposure constitutes an unacceptable risk.

We are fully aware of the factors such as hypoxia and hypovolaemia, but there is no clinical evidence that they occurred at any time in this patient. There was no known exposure to other hepatotoxic agents which could have exposed the child to additional risk factors. We believe that the clinical course and investigations show that this child did suffer halothane hepatitis.

Neutrophilia following the fourth administration of halothane may be relevant. An increase in the white blood count to a peak of 32.4×10^9 litre^{-1} (84% neutrophils) was noted following the second halothane anaesthetic. This is a greater increase than would be expected following major surgery and may, in retrospect, have been significant.

The development of diabetes mellitus remains unexplained, but there was a history of this condition in the patient's uncle. We think that the diabetes was coincidental rather than directly related to her illness.

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HEPATITE A L'HALOTHANE CHEZ UNE FILLETTE

RESUME

Une fillette de 4 ans a développé une hépatite sévère après la quatrième administration d'halothane en l'espace de 5 mois. Elle était porteuse d'un anticorps circulant qui agissait spécifiquement contre des hépatocytes de lapins préalablement sensibilisés à l'halothane. La patiente guérit complètment de son hépatite mais 5 mois plus tard, développa un diabète sucré.

HALOTHANE-HEPATITIS BEI EINEM KLEINEN KIND

ZUSAMMENFASSUNG

Ein 4-Jahre altes Mädchen entwickelte eine schwere Hepatitis nach der vierten Halothane-Gabe innerhalb von 5 Monaten. Es zeigten sich bei ihm zirkulierende Antikörper, die spezifisch auf Kaninchen-Hepatozyten, die vorher mit Halothane sensibilisiert wurden, reagierten. Die Patientin erholte sich von der Hepatitis vollkommen, 5 Monate später jedoch erkrankte sie an Diabetes mellitus.

HEPATITIS POR HALOTANO EN UN NIÑO JOVEN

SUMARIO

Una niña de 4 años de edad padeció de una hepatitis aguda a raíz de la cuarta administración de halotano en un periodo de 5 meses. Se demostró que tenía un anticuerpo circulante que actuaba específicamente en contra de los hepatocitos de conejo previamente sensibilizados al halotano. La paciente se recuperó completamente de la hepatitis, pero 5 meses más tarde, desarrolló diabetes mellitus.

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INADVERTENT INJECTION OF THIOPENTONE TO THE BRACHIAL PLEXUS SHEATH

A case report

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SUMMARY

Fifteen millilitre of 2.5% thiopentone was accidentally injected via the axillary route to the brachial plexus sheath of a fit 17-yr-old male. Mild discomfort was experienced during the injection. Immediate treatment included injection of normal saline 40 ml and 1% lignocaine with adrenaline (1 : 200 000) 40 ml to the sheath. A stellate ganglion block was also performed and dexamethasone administered i.v. The patient experienced moderate local pain and tenderness during the subsequent 3 days, but no neurological or vascular sequelae. Guidelines for the prevention and treatment of this mishap are suggested.

A rarely described hazard of local anaesthesia is the inadvertent injection of solutions other than the intended local anaesthetic. A patient is reported in whom a solution of 2.5% thiopentone was injected around the brachial plexus. This was followed by an uneventful and complete recovery.

CASE REPORT

A fit 17-yr-old male, weighing 62 kg, was to undergo surgery to the left thumb. A brachial plexus block by the axillary perivascular approach was planned (Winnie, 1974).

Two 20-ml disposable syringes were filled with a solution of 1% lignocaine with adrenaline 1 : 200 000 and placed unlabelled in an area used to prepare drugs for local and general anaesthesia. The sheath was entered with ease using a 23-gauge needle attached to an extension set (MacEvilly, 1980). Paraesthesiae were not elicited and confirmation of the position of the needle in the sheath was obtained by the characteristic feel of penetrating the sheath and by oscillations of the needle on the axillary artery. Following aspiration, 15 ml of solution was slowly injected. The patient complained of mild pain at the site during the early part of the injection, but this was not considered unusual at the time. However, when the discomfort persisted, it was realized that the solution being injected was 2.5% thiopentone, prepared earlier for another patient. Forty millilitres of the prepared local anaesthetic solution was injected and the needle withdrawn from the sheath. Five minutes later the axillary sheath was again entered and 40 ml of 0.9% sodium chloride injected to dilute the thiopentone. A left stellate ganglion block was also performed using 0.25% bupivacaine 15 ml injected by a paratracheal approach (Atkinson, Rushman and Lee, 1977). Successful motor, sensory and sympathetic blockade occurred, but the planned surgery was postponed, dexamethasone 8 mg administered i.v. and the arm elevated.

Four hours later the patient has some paraesthesiae in the fingers and motor function had returned to normal. He was discharged later that day after complete recovery and advised to contact the hospital should he experience any untoward symptoms.

When the patient was readmitted 2 days later, he reported having had moderate pain and tenderness in the axilla since discharge. There was no sensory or motor abnormality on examination and the planned surgery was carried out under general anaesthesia. The axillary discomfort had disappeared on discharge the following day. The patient was seen by one of us (S. A. T.) 4 weeks later and again there was no deficit.

DISCUSSION

Thiopentone is cytotoxic (Buckspan et al., 1978) and has been known to cause tissue damage when administered by a variety of routes. Thrombosis

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and thrombophlebitis can result from i.v. injection (Hutton and Hall, 1957; Hästbacka et al., 1966; O'Donnell, Hewitt and Dundee, 1969) and the varying degrees of damage, from pain to gangrene of a portion of a limb, that may occur after intra-arterial injection are widely appreciated (Van Der Post, 1942; MacIntosh and Heyworth, 1943; Cohen, 1948; Stone and Donnelly, 1961; Engler et al., 1967; Klatte, Brooks and Rhamy 1969; Lynas and Bissett, 1969; Albo et al., 1970; Ready, 1972; Dundee and Wyant, 1974). In addition, subcutaneous injection can result in tissue necrosis (Davies, 1966, 1971, 1979) which may require skin graft (Gaze, 1978; Coote and Abeysiri, 1979) and isolated damage to nerve and muscle can occur (Davies, 1966, 1971, 1979), particularly to the median nerve (Pask and Robson, 1954). A notable feature in many of these reports is a latent period of up to 2 weeks after injection before the appearance of any tissue damage.

In view of the known proximal spread of solutions in the axillary sheath (Winnie et al., 1979), there was immediate concern in this case about widespread neurolytic damage. Vascular damage from the injection of thiopentone around the axillary artery was also possible.

There is no previous report of accidental injection of thiopentone around the brachial plexus. A single case report of accidental extradural injection has been described (Forestner and Raj, 1975) which was treated by dilution and recovered with no neurological damage. The brachial plexus perivascular space is analogous to the extradural space in that there is a plexus of nerves surrounded by a fascial sheath and a similar outcome could be anticipated after injection of thiopentone to either space.

Active management must be taken after misplaced injection has occurred because of potential tissue damage by thiopentone solutions. We would suggest the following measures:

(1) Dilution of injected solution by isotonic saline or dextrose solution.

(2) Injection of local anaesthetic solution (without adrenaline) to provide further dilution and also to induce local hyperaemia and hasten absorption of thiopentone.

(3) Although not given in this case, injection of hyaluronidase into the area may aid the dispersal and more rapid absorption of solution.

(4) Systemic or local steroids have been shown to minimize tissue destruction by thiopentone (Buckspan et al., 1978) and should be administered.

(5) If vascular damage is suspected, sympathetic blockade by brachial plexus or stellate ganglion block should be considered.

(6) Symptomatic measures include elevating and resting the limb and analgesics as required.

There are a number of specific measures which may be taken for the future prevention of this type of mishap. A separate sterile tray for regional procedures would reduce the risk of drugs intended for i.v. use being accidentally injected elsewhere and would also encourage a more careful technique by the operator. The need for careful preparation and labelling of solutions for injection must be emphasized. Adhesive tape or self-adhesive labels on which are printed frequently used anaesthetic drugs are now widely available and can be wall-mounted to facilitate their use (Carrie, 1975; Dunkin, 1978). The use of glass-barrel syringes for all regional blocks has also been recommended (Kennedy, 1980). Finally, all injections of local anaesthetic agents should be made slowly, holding frequent conversation with the patient during the injection to elicit any unusual symptoms that may arise.

The reporting of mishaps such as described should be encouraged, since they serve as useful reminders of the constant vigilance required of all anaesthetists. In addition, wider knowledge of their natural history can lead to a more rational approach to therapy when such events do occur.

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INJECTION ACCIDENTELLE DE PENTOTHAL DANS LA GAINE DU PLEXUS BRACHIAL

Rapport sur un cas

RESUME

Quinze millilitres de pentothal à 2,5% ont été injectés accidentellement par voie axillaire dans la gaine du plexus brachial d'un homme sain de 17 ans. Cette injection s'est accompagnée d'un léger malaise. Le traitement immédiat a comporté l'injection de 40 ml de chlorure de sodium isotonique et de 40 ml de lignocaïne à 1% adrénalinée (1 : 200 000) dans la gaine. On a également fait un bloc du ganglion stellaire, et de la dexaméthasone a été administrée par voie intraveineuse. Pendant les 3 jours suivants, le malade a eu une douleur et une inflammation locales modérées; mais pas de séquelles neurologiques ou vasculaires. On suggère quelques grandes lignes pour la prévention et le traitement de cet accident.

UNBEABSICHTIGTE INJEKTION VON THIOPENTAL IN DIE BRONCHIALPLEXUSSCHEIDE

ZUSAMMENFASSUNG

Fünfzehn ml 2,5% Thiopental wurden versehentlich über die Axillarlinie in die Bronchialplexusscheide eines gesunden, 17 Jahre alten Mannes injiziert. Leichtes Unbehagen wurde während der Injektion verspürt. Die sofortige Behandlung bestand in einer Injektion von normalem Saline 40 ml und 1% Lignocain mit Adrenalin 1 : 200 000. Eine Stellatum-Ganglionblockade wurde durchgeführt und Dexamethason i.v. verabreicht. Der Patient litt in den folgenden Tagen unter lokalen Schmerzen mit lokaler Empfindlichkeit, hatte aber keine neurologischen oder Gefässstörungen. Richtlinien zur Verhütung und für die Behandlung im Falle eines solchen Zwischenfalles werden vorgeschlagen.

INYECCION ACCIDENTAL DE TIOPENTONA A LA ENVOLTURA DEL PLEXO TRAQUEAL

Un informe clínico

SUMARIO

Se inyectaron accidentalmente quince mililitros de tiopentona al 2,5%, a través de la ruta axiliar, a la envoltura del plexo braquial de un muchacho sano de 17 años de edad. Durante la inyección se experimentó una ligera molestia. El tratamiento inmediato incluyó la inyección de 40 ml de solución salina normal y de 40 ml de lignocaína al 1%, con adrenalina (1 : 200 000), a dicha envoltura. También se ejecutó un bloqueo del ganglio estrellado y se administró dexametasona por vía intravenosa. El paciente experimentó un resentimiento y dolor local moderado durante los tres días siguientes, pero no se presentaron secuelas vasculares o neurológicas. Se sugieren las directrices para la prevención y el tratamiento de este tipo de contratiempo.

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THE PERFORMANCE OF A SCAVENGING VALVE

P. A. FOSTER

SUMMARY

A simple, compact and lightweight device for coupling active scavenging systems to shrouded breathing system valves is described. Provided a scavenging minute flow rate greater than the expired gas volume is available, the unit can handle automatically changes in both variables. Optimal function is achieved with scavenging flows from about twice the discharged gas flow to about 50 litre min^{-1}. At these flows the valve can accommodate the outflow of gas-driven ventilators where driving gas and circuit gas are discharged through the same port. There is no interference with expiratory valve function in the event of scavenging failure.

The valve described appears to be the most compact, simplest and easiest to use of those currently available for coupling active scavenging systems to shrouded expiratory valves. The model tested is manufactured as a lightweight polycarbonate moulding and needs no adjustment. This flow meter was found to be accurate at the subatmospheric pressures used.

The design is based on a circular body in which two lightly loaded disc valves A and B are held against knife-edge seats by a common spring (fig. 1). The two seats are of differing diameter.

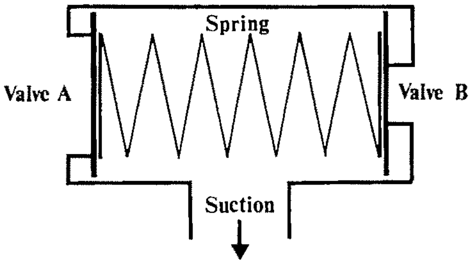

FIG. 1. Basis of a differential opening pressure valve.

When a negative pressure is applied within the body the disc of the larger diameter seat (A) opens first since the force applied to the disc is proportional to the area within the circumference of the valve seat. The difference in opening pressures of the two valves is thus set by the difference in seat diameter. Once the larger diameter valve A opens, the common spring, being compressed, positively seats the smaller diameter valve B.

Valve A is open to atmosphere so that, when it is opened by applied suction, pressures greater than atmosphere will be required to open B. Valve B is directly coupled to a suitable shrouded expiratory valve on an anaesthetic circuit. In the manufactured form this coupling piece is of 30 mm i.d. and fits a Penlon Mark II duct expiratory valve (fig. 2).

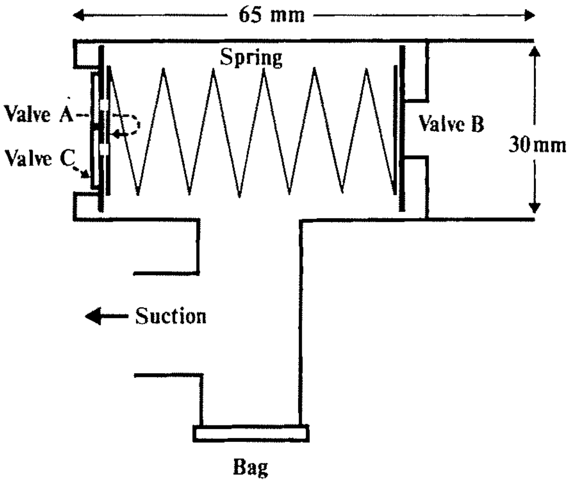

FIG. 2. Practical execution of the scavenging valve with fail-safe valve and indicator bag.

Provision is made to mount a 1- or 2-litre breathing bag close to the valve body in the suction line. This bag suffers peak flow discharges from the patient circuit, gives a visual indication that the unit is functioning, and damps oscillations that may arise in the spring and disc assembly. A variable restriction is provided in the suction line for use with very high volume dis-

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placement sources (greater than 100 litre min^{-1}). Otherwise the valve functions efficiently on any scavenging flow greater than the volume of anaesthetic gas dumped, up to at least 100 litre min^{-1}.

When in use, the patient valve opens as gas discharges from the patient circuit and this gas mixes with the entrained air. Should the peak flow from the patient circuit much exceed the scavenging flow, the valve discs and spring assembly toggle across to close the air entrainment valve, rebounding as the flow decreases.

Should the scavenging flow fail, expired gas may blow straight through the valve through a lightly loaded silicone rubber flap valve on the larger disc valve A (valve C) (fig. 2).

The effectiveness of this valve in reducing atmospheric pollution has been reported elsewhere (Moyes, Cleaton-Jones and Foster, 1980; Moyes et al., 1981). This account gives details of the static and dynamic function in the laboratory.

METHOD

Two manometer tubes were set up in the valve, one within the body and the other upstream of the patient valve B. Both were connected to Sanborn 267 BC transducers coupled to Hewlett–Packard 350–1100C preamplifiers and pen writers, calibrated to give full scale deflection of 10 cm at a pressure of 1 cm H_2O.

Oxygen, representing expired gas, was supplied to the patient side of the valve from a calibrated flowmeter (Gapmeter) over a range of 0–25 litre min^{-1}. The scavenge port was connected through a calibrated flowmeter (0–100 litre min^{-1}) via a variable restriction to a suitable high displacement suction source.

The use of oxygen as the "expired" gas in an air entrainment valve allows the dynamic performance to be followed by monitoring oxygen concentrations. A Centronic 200 MGA mass spectrometer was used.

Breathing patterns were produced using an Oxford volume cycled ventilator (Penlon) the output of which had been calibrated against an Ohio 840 spirometer. The ventilator inflow gas was always pure oxygen.

The following were measured (tables I and II):

(1) The opening pressure of the air admitting valve A with different scavenging flow rates (table I).

(2) The opening pressure of the silicone flap valve on valve disc A against different flow rates (table I).

(3) The opening pressures of patient valve B at different flow rates in the absence of a scavenging flow (table II).

(4) The total resistance through the valve to atmosphere in the absence of a scavenge flow (table I).

(5) The resistance to various constant flows through patient valve B at various scavenging flows. (The common spring between valves A and B results in an interaction between the two flow rates (table II).)

(6) The dynamic resistance of valve B under simulated clinical conditions with intermittent "expired" flow. An Oxford ventilator was coupled through breathing hoses to the patient valve B. Inflation times were set to 1 s, the volume to 1000, 750 and 500 ml and rate to 20 b.p.m. Pressures were monitored within the valve.

TABLE I. *Pressures across various components of the valve at different flow rates*

Flow rate (litre min^{-1})	Valve A (cm H_2O)	Valve C (cm H_2O)	Total expiratory resistance without scavenging (valves B and C) (cm H_2O)
5	—	0.1	0.21
10	0.37	0.18	0.47
15	—	0.28	0.69
20	0.6	0.38	0.86
25	—	0.5	0.93
30	0.75		
40	1.0		
50	1.25		
60	1.4		
70	1.5		

TABLE II. *Resistance to expiratory flow (cm H_2O) at various scavenging flows*

Scavenging flow rate (litre min^{-1})	Expired gas flow rate (litre min^{-1})						
	2.5	5.0	7.5	10	15	20	25
0	0.1	0.31	0.4	0.51	0.64	0.8	0.96
10	0.08	0.17	0.27	0.36	0.48	0.67	0.72
20	0.12	0.23	0.27	0.35	0.44	0.51	0.55
30	0.20	0.29	0.28	0.35	0.44	0.54	0.54
40	0.36	0.44	0.47	0.38	0.46	0.54	0.56
50	0.47	0.56	0.53	0.49	0.46	0.55	0.61
60	0.54	0.64	0.60	0.57	0.60	0.66	0.73
70	0.60	0.66	0.65	0.64	0.62	0.75	0.80
80	0.65	0.72	0.70	0.66	0.66	0.78	0.82

(7) Using the same ventilator the appearance of leakage of "expired" gas across the valve to atmosphere was sought by placing a sampling tube 1 cm above the centre of the valve disc A and recording the oxygen concentration with varying "expired" gas flow rates and scavenging flows (the expired gas being pure oxygen).

RESULTS AND DISCUSSION

The findings in the various static tests are summarized in tables I and II. In table II the figures are the averages of values obtained during increasing and decreasing scavenging flows. With larger scavenging flows expiratory resistance will be greater because the common spring is slightly more compressed, so that readings from high flows are slightly higher. This pattern is reflected throughout all the static readings when the lowest expiratory resistances are seen when expired flow is similar to scavenging flow. However, the dynamic performance was such that the smallest resistances are found when the scavenging flow is 50–100% greater than the expired flow, thus matching well the 25–50 litre min^{-1} scavenging flows found in most systems. An idea of the ratio of scavenging flow to the expiratory flow is obtained from the degree of filling of the bag which should, preferably, empty completely before the end of each breathing cycle.

In the dynamic tests with a ventilator a consistent pattern of performance emerged when the following applied: (a) flow through the patient valve; (b) pressure at the patient valve (0–1 cm H_2O); (c) pressure within the valve body (0–1 cm H_2O); (d) oxygen concentration in air over entrainment valve when the ventilator was set to deliver 500–1000 ml in 1 s with a 1 : 2 inspiratory/expiratory cycle.

At the start of expiratory flow, there is an increase of pressure behind the patient valve to about twice the normal opening pressure which lasts for about 20 ms before decreasing again. As the valve opens a peak flow is generated with maximum values up to about 2.5 times the mean flow, lasting less than 40 ms before levelling off with minor oscillations of up to ±2.5% about the mean.

This instantaneous peak flow is significant because flows in excess of scavenging flows could be generated with volumes larger than the 30 ml internal volume of the valve, and might cross to atmosphere if a buffer bag was not provided. This was studied by monitoring oxygen concentrations over the air entrainment valve. When the scavenging flow was the same as the mean flow, no oxygen leak across the valve was detected. Reducing the scavenging flow by 25% led to very brief increases in oxygen from 21 to ±30% for small parts of the expiration period. These coincide with the peak flow period and probably do not constitute "pollution" because the increase is localized by the air entrainment to the area over the valve disc. Significant oxygen build-up over the valve occurs as the scavenging flow decreases to near the average minute volume.

Testing at flows of 500–1000 ml s^{-1} represents the most severe test that is likely to be encountered in clinical use. Fresh gas flows seldom exceed 10 litre min^{-1} except perhaps when using Bain type circuits where up to 20 litre min^{-1} may sometimes be needed. Assuming that inspiration and expiration are equal, normal discharge rates are likely to be 20 litre min^{-1} or less and, exceptionally, 40 litre min^{-1}. If expiration is longer than inspiration, discharge flows are less. The volume and rigidity of the walls of the breathing circuit will also influence the peak flow. The test circuit was fitted with a small-volume rigid-wall plastic tube between ventilator and valve. When corrugated breathing hose was substituted, peak flows decreased.

The results show that this valve scavenges effectively with a pressure increase of not more than 0.5 cm H_2O at the expiration valve of an anaesthetic circuit.

The optimal performance judged by lowest operating pressures and efficient pollution control is achieved at scavenging flows in the region of 50–100% greater than the fresh gas inflow. Depending on the type of breathing system to be used and the fresh gas flows likely to occur, scavenging at the rate of 25–50 litre min^{-1} is indicated.

ACKNOWLEDGEMENTS

My thanks are due to Mr W. Z. Butler who converted the original ideas into Perspex, and to Prof. C. M. Conway and Mr R. Tennant of the Magill Department of Anaesthesia in the Westminster Hospital, London for their advice and generous assistance in the laboratory testing of the manufactured unit.

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PERFORMANCE D'UNE VALVE D'EVACUATION

RESUME

On trouvera ici la description d'un dispositif simple compact et léger pour coupler des systèmes d'évacuation active aux valves des circuits respiratoires enfouis. A condition de fournir un débit d'évacuation-minute supérieur au volume de gaz expiré, le dispositif peut faire face automatiquement à des variations des deux paramètres. Un fonctionnement optimal est obtenu avec des débits d'évacuation allant du double du débit expiré jusqu'à environ 50 litre min^{-1}. A ces débits, la valve peut traiter le debit de respirateurs mus par les gaz dans lesquels le gaz qui fournit la force motrice et le gaz du circuit respiratoire sont délivrés par la même entrée. Il n'y a pas d'interférence avec le fonctionnement de la valve expiratoire en cas de défaillance de l'évacuation.

BESCHREIBUNG EINES FRISCHGASVENTILS

ZUSAMMENFASSUNG

Ein einfaches, kompaktes und leichtes Frischgas-Spülsystem, das an die bei Beatmungsgeräten schwer zugänglichen Ventile angeschlossen werden kann, wird beschrieben. Bei der Vorgabe eines Spülgasflusses pro Minute, der grösser ist als das Atemminuten-Volumen, kann das Gerät automatisch beide Variablen steuern. Die grösstmögliche Wirkung des Gerätes wird erreicht, wenn das Spülgasvolumen pro Minute zweimal so gross ist wie das abgegebene, bis maximal 50 litre min^{-1}. Bei diesen Gasströmen kann das Ventil den Gasstrom vom gasgetriebenen Ventilator, bei dem das antreibend Gas und das Atemgas an der gleichen Stelle austreten, steuern. Wenn das Gasspülsystem versagt, gibt es keine Beeinträchtigung des Ausatemventiles.

PERFORMANCIA DE UNA VALVULA BARREDORA

SUMARIO

Se describe un dispositovo ligero, compacto y sencillo de acoplamiento de sistemas de expulsión activa a las válvulas de un sistema de respiración protegido. A condición que esté disponible un ritmo de flujo de expulsión por minuto mayor que el volumen de gas expirado, la unidad puede manejar automáticamente las modificaciones de ambas variables. La función óptima es lograda con flujos de expulsión de alrededor de dos veces el flujo de gas descargado hasta cerca de 50 litro min^{-1}. Con estos flujos, la válvula puede acomodar el flujo de los ventiladores accionados por el gas cuando el gas motor y el gas del circuito se descargan a través del mismo orificio. No hay interferencia alguna con la función de la válvula de expiración en caso de falla de la expulsión.

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CORRESPONDENCE

EXTRADURAL MORPHINE AND STOKES–ADAMS ATTACKS

Sir,—There have been several reports of respiratory depression after the extradural injection of morphine, but cardiac depression has been seen only after intrathecal injection and then in combination with respiratory depression (Liolios and Andersen, 1979; Davies, Tolhurst-Cleaver and James, 1980). We describe an extradural injection of morphine complicated by Stokes–Adams attacks without respiratory depression.

A healthy, 40-yr-old woman underwent hysterectomy; general anaesthesia included halothane. One hour before operation the patient received pethidine 50 mg i.m. and morphine chloride 4 mg in isotonic sodium chloride 25 ml through a lumbar extradural catheter. Morphine 4 mg in isotonic sodium chloride 10 ml was injected extradurally 2.5, 3 and 5 h later. The patient suddenly felt nauseated and fainted for 1 min, 4 h after the last injection. The continuously monitored e.c.g. indicated A–V block with a 15-s period of asystole and atropine 0.6 mg was given i.v. with immediate reversal to normal sinus rhythm. There were two similar attacks on the following day, 13 h and 15 h after the second of two doses of morphine 4 mg in sodium chloride 10 ml, which had been given 6 h apart. The patient did not receive further morphine extradurally and morphine dinicotinate ester (Vilan) was administered i.m. without complications for the next 2 days. A week later the patient was discharged without any evidence of cardiac disease.

The Stokes–Adams attacks were probably caused by increased parasympathetic activity from stimulation of the dorsal nucleus of the vagus as a result of the rather large dose of morphine. The interval of 4–15 h between the morphine injection and the cardiac depression is in accordance with that reported for respiratory depression following extradurally injected morphine. This indicates the same pharmacodynamic mode of action, but strangely enough, we did not observe respiratory depression.

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POSTERIOR FOSSA SURGERY

Sir,—We were depressed to read the survey of posture and ventilation by Campkin (1981).

The frequency of air embolism during neurosurgery in the sitting position depends on the diagnostic criteria, but has been said to be as high as 93% (Michenfelder, Miller and Gronert, 1972) with a mortality of up to 73% (Ericsson, Gottlieb and Sweet, 1964). Buckland and Manners (1976) studying 36 patients described a frequency of 33% with two deaths. To this is added the complication of hypotension which may embarrass cerebral blood flow in elderly patients or those whose cerebral circulation is already compromised by the pathology. In contrast the use of the prone or semi-prone position eliminates both these problems, borne out by the fact that there has been no death in this unit from air embolism since the adoption of this position.

It was stated that adopting the sitting position allowed the surgeon to orientate himself as the patient was in the same position as himself. If all surgeons adopted this idea can we expect to see surgeons in the supine or lithotomy positions? In our view the use of the sitting position with all its attendant risks should be limited to a few specific instances when the use of the prone position would necessitate excessive retraction. Surgeons and anaesthetists who favour the routine use of the sitting position and are currently investigating methods of detecting air embolism would be far better studying and practising techniques which use the prone position and thus allow them to eliminate this complication completely.

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MORBID OBESITY

Sir,—We read with interest the paper by Fox, Whalley and Bevan (1981) describing their experience with morbidly obese patients undergoing gastrointestinal bypass surgery, and would agree with many of their comments on preoperative assessment, operative management and the dangers of inadequate postoperative care. However, we would like to report our own, smaller, series in which we used a different approach to postoperative management.

During the years 1976–80, 17 female and five male patients with a mean age of 32 yr (range 20–53 yr) and a mean weight of 122 ± 6 kg underwent gastrointestinal surgery for morbid obesity (jejuno–ileal bypass (15), gastroplasty (seven)). General anaesthesia and controlled ventilation was used in all patients. FI_{O_2} was adjusted in accordance with repeated arterial blood-gas estimations and anaesthesia maintained with intermittent fentanyl and nitrous oxide in oxygen. When the oxygen requirement was high, 0.5% halothane was added. Neuromuscular blockade was achieved with either pancuronium or tubocurarine.

The second patient in the series died 24 h after completion of surgery following an episode of cardiorespiratory insufficiency, and subsequent patients were admitted to the Respiratory Intensive Care Unit for a period of elective mechanical ventilation until cardiovascular stability in the sitting position was attained.

Control of ventilation in these patients was satisfactorily achieved by i.v. morphine given via an infusion pump in a dose of 5–10 $mg\,h^{-1}$. Six patients also required an infusion of Althesin as they remained restless despite indicating that they were pain-free. Neuromuscular blocking drugs were avoided.

On the first day after operation, weaning from mechanical ventilation presented no difficulty and after tracheal extubation, all patients were well enough to return to the general ward. Controlled oxygen therapy and vigorous chest physiotherapy were continued for several days. Only one patient developed a respiratory infection after operation, with pyrexia, purulent sputum and radiological change.

Careful selection of patients for this type of surgery excludes the older grossly obese patient with associated disorders (Fisher, Waterhouse and Adams, 1975), but this type of patient may well present for emergency abdominal surgery in units with little experience of the problems associated with surgery and anaesthesia in morbid obesity. Like Fox and his colleagues, we feel that all grossly obese patients undergoing major surgery should be managed in an Intensive Care Unit after operation. However, we are of the opinion that a period of elective ventilation after operation, controlled by means of a narcotic infusion ensures pain relief and good oxygenation, and offers a satisfactory alternative in the management of the grossly obese patient presenting for elective or emergency surgery.

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LARYNGEAL MICROSURGERY

Sir,—Oliverio, Ruder and Abramson (1981) question our contention that this is a potentially dangerous technique and state that "spontaneous ventilation . . . is unacceptable for carbon dioxide laser surgery".

In our original letter (Steward and Fearon, 1981) we described our technique of light general anaesthesia combined with topical analgesia and continued spontaneous ventilation for laryngeal surgery and other endoscopic procedures on the airway. We have used this technique for more than 200 patients undergoing laser surgery to the larynx, and find the operating conditions to be excellent. The vocal cords, contrary to the statement of Oliverio and colleagues, are totally immobile during this type of anaesthesia. The access of the surgeon is completely unimpeded. The safety of this technique is confirmed by the fact that we have encountered no serious complications during operation. Talmage (1981) reports a similar experience in a series of patients undergoing laser surgery.

We would repeat our warning that the use of jet ventilation via a cannula into the trachea appears to be a very dangerous practice. We question the use of this technique when at least equally satisfactory operating conditions can be achieved by other means.

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Talmage, E. A. (1981). Endotracheal tube is not necessary for laryngeal microsurgery. *Anesthesiology*, 55, 382.

Sir,—I have read with interest the letter of Oliverio, Ruder and Abramson (1981) in which they recommend the injection of pure oxygen through the vocal cords during laser surgery. I know of two instances when patients were ventilated with pure oxygen, using the Sanders injector during bronchoscopy for coagulation of tracheal lesions under diathermy, in which the oxygen caught fire with a gust of flames sprouting from the bronchoscope. The bronchoscopists' hair and eyebrows were singed, and it is fortunate that they should both have been wearing spectacles.

Recently, another patient literally blew up when oxygen was injected in front of the cords during laser surgery of the larynx. This resulted in major pulmonary, tracheal and laryngeal burns, requiring tracheotomy in the first instance, and tracheal resection later.

What is true of bronchoscopy must be equally true of laryngoscopy. I do not question their ventilating technique, but the use of pure oxygen, and suggest that a mixture of 50% oxygen in nitrogen, which is not inflammable, should be preferred.

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REFERENCE

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CARBON DIOXIDE HOMEOSTASIS AND CIRCLE SYSTEMS

Sir,—Reliable mathematical descriptions of carbon dioxide homeostasis in circle systems without carbon dioxide absorption may be of considerable interest for the evaluation of the efficiency of different systems. Recently Schoonbee and Conway (1981) published such a study. Unfortunately the interpretation of their results causes some difficulty. In figures 2 and 3 (System I) they demonstrate the correlation between the end-tidal carbon dioxide concentration ($F\mathrm{E}'_{\mathrm{CO_2}}$) and the minute ventilation ($\dot{V}\mathrm{E}$) using a constant fresh gas flow ($\dot{V}\mathrm{F} = 5$ or 6 litre min^{-1}), and a constant carbon dioxide "production" ($\dot{V}\mathrm{CO_2} = 224$ ml min^{-1}). However, the regression equations contain four variables: $F\mathrm{A}_{\mathrm{CO_2}}$ (alveolar concentration), $\dot{V}\mathrm{CO_2}$, $\dot{V}\mathrm{F}$ and $\dot{V}\mathrm{AE}$ (alveolar ventilation). I suppose $F\mathrm{A}$ equals $F\mathrm{E}'_{\mathrm{CO_2}}$, but the authors do not explain how they derive $\dot{V}\mathrm{AE}$. Their system contains a fixed deadspace of 160 ml, but, as far as I can see from the figures and the equations, this deadspace value has not been used for the calculations of $\dot{V}\mathrm{AE}$.

Using $\dot{V}\mathrm{CO_2}$ 224 ml min^{-1} and $\dot{V}\mathrm{F}$ 5 litre min^{-1} the mean carbon dioxide concentration in the gas vented from the circle is 224/5224 = 0.043. In a steady state the end-tidal concentration must always be greater than 4.3%, but for System I in figure 2 both the regression line and some of the measurements are less than this value.

Nevertheless, the study of Schoonbee and Conway shows that the carbon dioxide homeostasis for the two systems is very dependent on the tidal volume. This is not surprising for a circuit in which the fresh gas inlet is placed away from the patient. Here "old gas" is used during the first part of the inspiration. In the system described by Ladegaard-Pedersen (1978), both the fresh gas inlet and an undirectional valve are placed close to the patient. The inital part of the tidal volume will always be fresh gas. Without hyperventilation about 90% of the gas vented from the circuit is alveolar gas. The fresh gas demand is about 60 ml kg^{-1} min^{-1}.

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Schoonbee, C. G., and Conway, C. M. (1981). Factors affecting carbon dioxide homeostasis during controlled ventilation with circle systems. *Br. J. Anaesth.*, **53**, 471.

Sir,—Dr Ladegaard-Pedersen confuses the statistical and physiological interpretation of experimental data. The regression equations contained in our paper were not derived in order to demonstrate the mode of action of the systems studied, but to show that under the stated conditions of use these systems behaved consistently, and that differences in performance could be ascribed to differences in system geometry. The equations were derived using one dependent variable ($F\mathrm{A}_{\mathrm{CO_2}}$, assumed equal to $F\mathrm{E}'_{\mathrm{CO_2}}$) and two independent variables, alveolar ventilation being calculated from tidal volume, deadspace and respiratory frequency and fresh gas flow being either 5 or 6 litre min^{-1}. Carbon dioxide output was taken as constant. The equations were not constrained to a minimum value of $F\mathrm{A}_{\mathrm{CO_2}}$, and at high values of either $\dot{V}\mathrm{F}$ or $\dot{V}\mathrm{AE}$ will inevitably give $F\mathrm{A}_{\mathrm{CO_2}}$ values less than this minimum. The data point below the theoretical minimum we ascribed to the experimental errors inherent in the attempted accurate delivery of gas volumes and measurement of gas concentrations.

The circle system referred to by Dr Ladegaard-Pedersen resembles the F arrangement of Eger and Ethans (1968). We examined the two most widely used configurations of circle system components. As it was part of our thesis that system geometry influences circle system behaviour, we are not surprised that the arrangement he uses differs in performance from those we tested. The description of the performance of his system (Landegaard-Pedersen, 1978) reveals that throughout the study a constant respiratory frequency was used. Whilst we are not in a position to make any informed comments, we would speculate that, like the arrangements we examined, that particular form of circle system would change its performance in response to changes in respiratory frequency.

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Br. J. Anaesth. (1982), 54, 367

BOOK REVIEWS

The Quantitative Practice of Anaesthesia: Use of Closed Circuit. By Harry J. Lowe and Edward Ernst. Published (1981) by Williams & Wilkins, Baltimore. Pp. 234; illustrated; indexed. Price not stated.

There is every indication that closed and low-flow breathing systems in anaesthesia are enjoying something of a renaissance. If there is a single obvious impediment to this it is that a generation of anaesthetists has been trained in the administration of comparatively safe inhalation anaesthesia using systems which have minimal or no rebreathing; thus the inspired concentration of a volatile anaesthetic is thought to be easily predictable from the vaporizer setting. This, together with the concept of MAC as a measure of dose has lessened the need for skill in recognizing the signs of anaesthesia. If this deficiency can be corrected—and there are many reasons in addition to the use of closed and low-flow systems to justify the attempt—there is no reason why the use of low flow systems, particularly where oxygen is the sole carrier gas, should call for any great fuss. Even the use of nitrous oxide with oxygen as the carrier gas can be quite safe if the pattern of nitrous oxide uptake to the tissues is understood and an oxygen monitor is used.

I have laboured these points because I believe that closed or low-flow system anaesthesia is not too difficult and can be fun. Having perused their book I am satisfied that Drs Lowe and Ernst would agree with me on the latter, but within the book they have elevated what should be a relatively simple art to an elaborate science and some of their text is likely to scare off all but those who have an advanced capability in mathematics. I do not wish to suggest that there is nothing of value in this text because the theoritician will find much that is of interest and a good deal to argue about; Drs Low and Ernst, in spite of their elaborate text, confine themselves to an ideal patient considered as a series of tight compartments which do not leak.

In the preface it is implied that the text is designed to encourage the wider use of closed and low-flow systems. If it is to do that, I would recommend that ordinary mortals might begin at page 153. Here they will learn that, in an anaesthesia machine, the source of gases might come from a central line or from tanks attached to the machine—trivial perhaps, but a blessed relief after the mental gymnastics that were necessary to follow all that preceded it.

There is much in this book which will reward careful study because the text extends beyond the immediate considerations of closed and low-flow systems and reviews fundamental aspects of the uptake and elimination of gaseous and volatile anaesthetics. Some of the tables will be useful sources of reference. My disappointment is that the authors have failed to define their target readership adequately. In additon there is a lack of balance: Dr Low's demonstration that the cumulative vapour requirements in a closed system are proportional to the square root of elapsed time is of interest, and occasionally of practical value. It does not deserve one-sixth of the space allocated to a brief introduction chapter of the history of closed-circuit anaesthesia or a 31-page chapter within the main text.

Alastair A. Spence

Advances in Neurology, Volume 28, Brain Edema: Pathology, Diagnosis, and Therapy. Edited by J. Cervos-Navarro and R. Ferszt. Published by Raven Press, New York. Pp. 511; illustrated; indexed. Price $65.28.

This is an unusual book, in that it consists not only of papers given at a scientific conference (in this case, 1979—Earnst Reuter Symposium), but also a number of chapters which review the current position in different areas of research in brain oedema. I began to read it expecting that this would be a thinly-veiled disguise to put across another Conference Proceedings, but in fact found the book to be most worth while.

The following subjects are amongst those covered in these review chapters: Quantification of brain edema, Intracranial pressure monitoring, CSF Formation and absorption, Ischaemic brain edema, Metabolic basis of brain edema, Biochemistry of brain edema and a fascinating chapter by Klatzo and colleagues on the time-course of the resolution of brain edema. It was interesting to read that the vasogenic oedema of experimental cold injury mainly resolves between 4 and 7 days, which agrees rather well with clinical experience in the management of severe head injury.

The book finishes with several chapters on the treatment of brain oedema. This book is produced on high-quality paper with excellent illustrations and is recommended to those anaesthetists who wish to have more than a basic understanding of this important type of brain pathology.

D. G. McDowall

Electrical Safety in Hospitals. By C. S. Ward. Published (May, 1981) by Henry Kimpton, London. Pp. 197; illustrated; indexed. Price £10.25.

The search for safe electromedical equipment has led to a steady series of developments in design and circuitry intended to protect the patient from the hazards of electric shock and burns in the event of faults developing in the equipment or in the event of misuse. Nevertheless, the education of the user of the equipment is of equal importance, particularly in the case of apparatus such as the diathermy or the defibrillator with which large electric currents and voltages are deliberately applied to the patient. Dr Ward's book is a valuable contribution to the problem of education in the safe use of electromedical equipment. The book is concerned primarily with the question of electrical safety in hospitals, which it covers in a comprehensive manner and with medical readership in mind. The subject matter is somewhat broader than that suggested by the title, as the earlier chapters are devoted to an examination of the nature of electricity, its properties and the behaviour of electrical components. This treatment is necessarily sketchy in places. A detailed description of the detection of biological electrical potentials is not included, but the book covers in depth all techniques involving the elective application of electric potentials to the body as well as certain salutory lessons drawn from incidents involving non-elective application. Anyone who is concerned to know the reasons behind the various operating procedures of electromedical equipment and who is concerned to use it safely will find the later chapters well worth reading, even if the introductory material is heavier going.

P. B. Davis

How to Understand Acid–Base. A Quantitative Acid–Base Primer for Biology and Medicine. By Peter A. Stewart. Published (1981) by Elsevier North Holland Inc., New York and Edward Arnold, London. Pp. 186; illustrated; indexed. Price £14.00.

This monograph aims to show what factors determine hydrogen ion concentrations in body fluids. Starting from considerations of water it develops the equations necessary to look at solutions of strong and then of weak electrolytes. The effects of carbon dioxide are then considered. The final chapter reviews the factors which maintain blood plasma hydrogen ion concentrations within a fairly narrow range.

In considering the factors determining the acidity of body fluids the author emphasizes three factors: the "strong ion difference", that is the difference in equivalents per litre between the sum of the strong cations and the strong anions; second, the dissociation constants for carbonic acid and third, the carbon dioxide tension. He uses standard physical chemistry equations to develop the interrelationships and has used a computer to solve a number of the more complex equations. Readers should be able to follow most of the equations; it will help to have access to good calculators and graph paper if the arguments are to be followed fully.

It is important to realize that this book is devoted only to factors determining hydrogen ion concentration. It does not deal with determinants of carbon dioxide tension or the concentrations of the various strong ions. It does not discuss the effect of alterations in hydrogen ion concentration. It should be used by those who wish to pursue the physical chemistry in depth.

The book is marred by two points. First, the symbols used are neither standard nor internally consistant. Thus carbon dioxide tension is Pc in the text and $P\text{CO}_2$ in the illustrations. Second, the illustrations seem to have been generated by a computer.

John Norman

Membrane Physiology and Cell Excitation. By B. Hendry. Published by Croom Helm Ltd. Pp. 159; illustrated; indexed. Price £9.95.

An understanding of the physiology and pharmacology relevant to the practice of anaesthesia requires a knowledge of the function of excitable cells; the anaesthetist spends most of his working life controlling, modifying and restoring normal cell membrane excitability. It is quite natural, therefore, that the author of this book looks to anaesthetists as a group of potential readers, as well as undergraduates for whom the book was primarily intended.

The book comprises a short well written and well illustrated account of the subject, and includes two rather brief chapters on mechanisms of general anaesthesia and on changes in cell membrane function in a few diseases. Its attraction lies in the clarity with which some of the more difficult concepts are explained, such as the reason for the electrochemical membrane equilibrium, and excitation–contraction coupling.

As an undergraduate text, it may well find favour, but for anaesthetists preparing for the primary F.F.A. it will be in competition with other established monographs.

One amusing feature was that as each page was turned it detached itself from the spine. The 80 loose leaves could be kept in a ring folder.

F. R. Ellis

Neurosurgical Anaesthesia and Intensive Care. By T. Victor Campkin and John Morris Turner. Published (1980) by Butterworths. Pp. 267; illustrated; indexed. Price £19.50.

Like neurosurgery, this book is meticulous, repetitious and, to an extent, prolonged and personalized. It is divided into four parts; physiology and pharmacology, basic considerations, clinical neuroanaesthesia and intensive care. Although abounding with fact and discussion, there is considerable repetition across the four parts.

In the first two sections, the authors have attempted to review relatively briefly the current state of neurophysiology. The result is a little disjointed and the discussion occasionally contradictory. Hence this not a text for the novice.

Each chapter has extensive references, although some are extremely historical. Many readers would take issue with the inclusion of cyclopropane and propanidid in a contemporary text on neurosurgical anaesthesia. Your reviewer pondered on whether a whole chapter on induced hypothermia was warranted.

With regard to the clinical section, I think few neurosurgical anaesthetists would use the foot for i.v. infusion, use a central venous line for administration of sodium nitroprusside, or hyperextend the wrist for radial artery cannulation. There was no discussion of the place for cannulation of the dosalis pedis artery. Most would also take issue with the suggestion that trimetaphan-induced hypotension for spinal surgery does not require an arterial line.

The chapter on induced hypotension left me rather anxious. Included in methods of inducing hypotension was guanethidine, a little used drug, but there was no significant discussion of the place of beta blockade, either with the premedication or preceding an agent such as sodium nitroprusside. I was particularly worried by the reference to the use of high positive airway pressure to induce profound hypotension. If this needed mentioning at all, it should have been made clear that such a technique is contraindicated in neurosurgical practice.

Although by and large the book is extremely comprehensive, it presents in parts a rather personal view. In the discussion of anaesthesia for aneurysm surgery, there is no mention of the head-up posture nor of cerebrospinal fluid drainage, a technique favoured by many neurosurgeons in this country. It was, however, pleasing to see a chapter devoted to neurosurgical anaesthesia in children.

In the section on intensive care, an area in which the role of the anaesthetist extends beyond giving an anaesthetic, your reviewer felt that scant attention had been given to care of the airway and avoidance of secondary insults following head trauma. Compared with our own practice, the authors were liberal in their use of i.v. fluids. The place of steroids in head injury is controversial. The authors expressed one view, that steroids should be given usually in conjunction with osmotic diuretics if increased intracranial pressure was present. Other well-researched experience shows steroids to be completely useless in this situation. Brain death was dealt with rather cursorily and particularly depressing was the statement (when brain stem death was confirmed clinically) "However, the EEG and hence hemisphere function should also be assessed by an experienced neurophysiologist."

The book is well laid out on beautiful paper with a minimum of typographical errors, although the printing is rather small. The great value of this book is that it is comprehensive and because of this it deserves a place in all medical libraries.

Sheila M. Willatts

Humidification of Anesthetic Gases. By J. Chalon, M. Ali, H. Turndorf and G. K. Fischgrund. Published by Charles C. Thomas, Springfield, Illinois. Pp. 138; illustrated; indexed; Price $17.50.

This monograph is the first to attempt to present humidification as the sole topic. The preface states that "the book is intended as a teaching manual for residents in anesthesiology and as a reference book".

Five sections cover an introduction to the principles, equipment and instrumentation, existing systems, new systems and a summary. The first of these concentrates a good deal of basic information, although the opportunity of presenting definitions of the terms used has not been taken. The measurement of humidity is outlined, but there is no mention of the calibration of humidity measuring instruments. The other two chapters in the first section describe the effects of humidity on tracheo–bronchial ciliated epithelium and the advantages and disadvantages of high inspired humidity. The content varies from clinical generalization to extracts from Chalon's original papers. Certainly, the newcomer will find difficulty in separating established fact from the views of the enthusiast. Nevertheless, the two chapters serve as a necessary appetizer for a diet of opinion recurring throughout the remainder of the book. At this early stage it is claimed that humidification "lowers post-operative pulmonary complication rate". The thesis is supported more than once by reference to "virtually a straight line" on a semi-logarithmic plot, where others might perhaps be more cautious. It is unfortunate that the authors deal dismissively with the literature on this matter since, as far as this reviewer is aware, there has been difficulty in establishing the efficacy and optimum values of humidity in anaesthetized patients.

The section on instrumentation discusses humidifiers and their associated breathing systems. Here, an otherwise lucid and helpful account is marred by over-emphasis on arrangements studied by the authors and by some unsupported statements which could be regarded as controversial. The second chapter in this section is helpful, although it is doubtful if the account of nebulizers could be said to add anything to the excellent presentation by Cushing and Miller in Safar's *Respiratory Therapy* published in 1965. Moreover, it contains oversimplifications, such as those referring to the possible effects of increasing gas flow, and a strange misconception about the Spence and Melville humidifier.

The opening chapter of the section on existing systems has less to do with humidity than with the characteristics of breathing systems. Professor Chalon and his co-workers have contributed greatly to the literature in this particular field and a fair summary of this is laid before the reader. However, it displays a few idiosyncracies, such as the use of the term "tube–bag systems" and is arguably less concise and informative than the reviews of Sykes or Conway. A case is made for greater use of the absorption canister (in a variety of adult and paediatric systems), whilst criticism of the Bain circuit is implied on the grounds that "No recent work from the inventors has as yet appeared in which $\dot{V}\text{CO}_2$ values have been reassessed". The closing chapter in this section offers some very sensible advice, particularly on paediatric applications, before wandering again into absorption systems.

Chapters 10, 11 and 12 speculate on new systems. Whether this is appropriate to a book with the aims stated in the preface is open to question, but the material presented is none the less interesting, being a distillate of the more recent work from Professor Chalon's laboratory. The summary section disappoints, but the bibliography might well be regarded as sufficient reason for buying the book.

The objectives have been achieved to a limited extent. The volume is well indexed and bound, but the paper is of poor quality and numerals on some of the original illustrations are difficult to read. Despite these criticisms, I enjoyed reading the book and would recommend it. Residents might find it esoteric in parts, and I doubt if its contents will succeed in changing the habits of the anaesthetist with a general, predominantly adult, practice. As a reference book it falls short, although with expansion of some chapters, more care with detail and fuller discussion, it could be very useful indeed.

Bernard Hayes

Anaesthetic Nursing. By C. J. Wallace. Published by Pitman Medical Ltd. Pp. 278, illustrated; indexed. Price £14.95.

The nurse's role in British anaesthesia is difficult to define. In some hospitals it is restricted to accompanying conscious patients and to recovery areas, whilst in others the nurse is more directly involved, acting as the anaesthetist's assistant throughout complicated and technical procedures. Although it is doubtful if the nurse anaesthetist will emerge in the foreseeable future in Britain, we already have an increasing number of anaesthetic nurses who provide invaluable support in all branches of anaesthesia. It is for these that this book has been written.

The first section describes in detail an anaesthetic nursing programme similar to those used as a guide for training in Oxford and Manchester. It is instructive to realize the breadth of knowledge achieved by trainees in these and other centres which have organized courses.

The rest of the book is arranged into four modules dealing with equipment, drugs, specific procedures and total patient care respectively. There is a useful index.

The first module is very well presented with many useful and clear line diagrams of commonly encountered apparatus. The author must have had difficulty in selecting from the wealth of clinical apparatus. This is reflected especially in the ventilation section, where she includes details of a comparatively uncommon ventilator. The second module deals, fairly superficially, with anaesthetic, analgesic and muscle relaxant drugs. The author has retained proprietary names, which are often used in text. It is surprising that she includes one and a half pages on methoxyflurane and only half a page on diethyl ether. Specific procedures in module four include cardiothoracic, ENT, obstetric, paediatric, ophthalmological and neurosurgical anaesthesia. This section provides the reader with a useful overall view of the bigger subspecialties and allows comparisons to be made. The last module contains much of clinical value, including monitoring and fluid balance.

The only significant deficiency is the absence of a discussion of the nurse's role in the treatment of many of the medical problems impinging on and caused by anaesthesia and surgery. Perhaps the books contains too little physiology to make such a discussion useful.

It can be anticipated that this book will be popular amongst nurses who are involved in anaesthesia and recovery areas. Their requirements differ from those of medical students and operating theatre technicians, and this book, written by a nurse, is for them.

F. R. Ellis

The Therapy of Pain. Edited by M. Swerdlow. Published by MTP Press Ltd. Pp. 250; illustrated; indexed. Price £16.95.

This is a welcome addition to the Current Status of Modern Therapy series and illustrates the need for "updates" on pain therapy rather than the large volume which may be out of date in 2 years.

Pain is a rapidly developing specialty and Mark Swerdlow has collected a number of authors who have each contributed widely in the field.

The neurological aspects of pain therapy are clearly and concisely laid out by Dr Wyke and it is a pleasure to realize how much psychiatrists can contribute if they become interested.

In the U.S.A. it may be true that a multi-disciplinary team is a permanent feature of pain centres, but in this country one could submit that it was unwieldy, time-consuming and not cost-effective in terms of salaries. Dr Lipton is undoubtedly setting his sights high in his theory on the management of the pain centre, but temporary involvement with other specialties may be an equally effective solution.

Nerve blocking, as is known, plays an enormous part in the control of chronic pain. The author of this chapter may be forgiven for accentuating the dangers of intrathecal phenol and indeed neurolytic blocks in general, but it should not be forgotten that, in skilled hands, the technique has brought relief to countless sufferers and thoroughly justifies its place in the armamentarium.

From the second neurosurgical contributor comes a very comprehensive survey of a neurosurgical contribution and it is formidable indeed. One could almost feel after reading this that it was negligent to be allowed to suffer pain.

Cancer pain and terminal pain have qualified for separate chapters in this book. Whilst no-one denies that cancer pain is the most distressing and demoralizing, it is generally well managed in this country and compared with chronic back pain, the specific treatment of which is hardly mentioned in this edition, is relatively easy to control.

Despite these minor criticisms, this is an excellent book and should find its way into the libraries of all those interested in this subject.

J. W. Lloyd

Spinal Cord Sensation. Edited by A. G. Brown and M. Rethelyi. Published (1981) by Scottish Academic Press. Pp. 341; illustrated; indexed. Price £15.

This book is composed of a series of papers presented at a Symposium "Sensory Processing in the Dorsal Horn" held in July 1980. The speed with which these proceedings has appeared is a result of using camera-ready techniques and the inevitable loss in printing quality is only really marked in some of the micrographic reproductions.

The book as a whole concerns itself with "present day" research activity in three major areas.

First, the structural and functional organizations of the dorsal horn itself are described, with a definition of what actually constitutes the dorsal horn. This is followed by a series of papers which illustrates the elegance and sophistication of the use of the technique of filling physiologically-characterized isolated fibres or dorsal horn cells with horse-radish peroxidase to determine their three-dimensional termination zones or their three-dimensional occupancy respectively, or of using the retrograde transport of horse-radish peroxidase injected into fibres projecting outside the spinal cord to determine the site of origin and type of their cells of origin.

Second, the current concepts on the pharmacology of the dorsal horn are presented. Of particular interest to the anaesthetist are the papers relating to the control of transmission in nerve fibres carrying potentially noxious information into the central nervous system and the present evidence attempting to unravel the pharmacology of this control.

Last, there is a small collection of papers relating to plasticity in the spinal cord.

In common with most proceedings of Symposia the papers range from the readily comprehensible to the almost incomprehensible and from the verbose to the telegraphic. However, the book does present, overall, a clear picture of the present research effort and some indications of future activity in spinal cord physiology and pharmacology and does contain a large number of key references to enable those who wish to explore this field to do so, and its low price should not deter many potential readers.

A. Angel

Chemical Diagnosis of Disease. Edited by S. S. Brown, F. L. Mitchell and D. S. Young. Published (1979) by Elsevier/North-Holland Biomedical Press, Amsterdam. Pp. 1384; illustrated, indexed. Price £74.75.

The object of this book is to provide an authoritative text on the interpretation of tests used in clinical chemistry. The editors, who are from Northwick Park Hospital in England and the Mayo Clinic, have assembled a glittering list of contributors to achieve this aim. Some of the world authorities include Siggaard-Andersen on hydrogen ions and blood-gases, Hales on glucose metabolism, Sandler on neurogenic amines, Lewis on lipids and McIntyre on calcium and magnesium. It is not surprising, therefore, that the overall standard is very high, but the book is flawed by the long delay between the completion of the chapters and publication. The references for many chapters cease in 1976 and several authors have added plaintive addenda briefly mentioning important advances since that date. The result of this long gestation period is that the content of several chapters is already becoming out of date.

If used selectively, this book will provide an excellent review of metabolic problems which the anaesthetist may encounter both clinically and experimentally. For example, perusal of the masterly chapter on liver function by Jones and Berk will enable the anaesthetist to appraise critically published studies on the effects of anaesthetic agents on hepatic metabolism. One of the Editors, Professor Young from the Mayo Clinic, has contributed a fascinating chapter on biological variability. This includes the effect of diet, climate, exercise, noise, blindness, coughing and even caffeine and alcohol (particularly relevant for anaesthetists) on the concentration of the constituents of body fluids.

The book contains few errors, has a good index and is attractively presented. Every anaesthetic department should have a copy and *use it.*

G. M. Hall

Anaesthesia For Cardiac Surgery and Allied Procedures (2nd edn). By M. A. Branthwaite. Published (1980) by Blackwell Scientific Publications, Oxford and London. Pp. 209 + index, foreword and prefaces; illustrated; indexed. Price £12.50.

The second edition of this excellent monograph is now well established in the medical bookshops, and this is hardly surprising.

It has been said that the second edition of a textbook is usually the best. Certainly the second edition of Dr Branthwaite's book represents a careful improvement of an already very good first edition. The slightly expanded text (some 16 pages have been added) continues all the notable features of the first edition. The well organized and thoughtful content, the classification by subject of the references quoted after each chapter and of course the author's lucid style, reinforced by the clarity of the print and paper, are still here and are worthy of a further mention.

Changes are of two kinds. First, the book is, naturally enough, brought into line with changing patterns of disease and the changing perceptions of the cardiac surgeon and all those concerned with the care of patients with heart disease. Dr Branthwaite refers to these changes briefly in the preface: the increasing importance of ischaemic heart disease in surgical practice and the growing understanding of the possibilities for the protection of the myocardium in the perioperative period, among others.

Secondly, the chance has been taken to improve the existing text either in detail, perhaps by the alteration of a word or two, or where thought appropriate by expansion or modification on a larger scale. Close examination suggests that every part of the book has been given meticulous consideration. While there remain one or two topics which the individual reader might wish to see expanded further, one must respect the author's stated view that this would be inappropriate. This done one can accept the book for what it is—surely an essential and enjoyable part of any serious student's reading.

M. D. Hargreaves

Management of Head Injuries. By B. Jennett and G. Teasdale. Contemporary Neurology Series. Published by F. A. Davis Company, Philadelphia. Pp. 361; illustrated; indexed. Price £22.50.

This book was expected and generally succeeds in presenting the current state of the art in the management of head injuries. From the anaesthetists' point of view, it is important to note that 83% of brains in a Glasgow series had pathological evidence of increased intracranial pressure and 91% showed ischaemic brain damage. Many of these brains had associated haematoma.

The dynamic pathology of the brain, its metabolism and "brain protection" are discussed superfically; barbiturates and hypothermia merit only half a page each. Other important drugs are not mentioned.

Better chapters cover epidemiology, structural pathology and assessment of unconsciousness. There is clear differentiation between brain death and the vegetative state. The investigation of head injury is well described with perhaps unnecessary scepticism about the value of intracranial pressure monitoring. The authors seem more influenced by the statistical results in patients in whom intracranial pressure was monitored than with the rationale of monitoring the physiological variables which various treatment regimes are designed to correct. Nevertheless, the use of intracranial pressure monitoring is recommended after the removal of intracranial haematoma because of the frequency of subsequent increases of pressure.

Cerebal blood flow, e.e.g. and somatosensory evoked potentials have, as yet, proved disappointing tools and the hope is expressed that biochemical markers of brain damage will prove more satisfactory.

Cardiorespiratory monitoring is outlined briefly but marred by several attacks on anaesthetists and their judgement, such as "the consequences of change in respiratory function will be different in patients who are breathing spontaneously, whose chemoreflex activity is preserved, than in those whose ventilation is controlled or assisted. Failure to acknowledge this physiological fact may account for some of the differences between the statements of anaesthetists on the one hand and surgeons on the other". Further, when discussing the use of controlled ventilation: "Most neurosurgeons (as distinct from anaesthetists) probably prefer to use controlled ventilation very selectively". Fortunately Jennett and Teasdale probably represent a minority of neurosurgeons, many of whom show more humility and less bombast when jointly planning the therapeutic objectives and measures in the acute management of severe head injuries.

The first aid description of airway care is less than would be expected from trained ambulance personnel and talk of intermittent nasopharyngeal suction and nursing in the semi-prone position as adequate or safe "particularly in children" is simply nonsense. The rules and indications for endotracheal intubation are set out, including advice on the competence of the intubator. This seems no more relevant in this book than would discussions on the competence of those surgeons performing craniotomy. Advice on ventilatory care implies that controlled ventilation should be avoided at all costs and notes that "a combination ventilation of I.M.V. and P.E.E.P. may permit management of some chest injuries without recourse to full controlled ventilation". The important areas which are not appreciated by the authors are the dangers of poorly controlled ventilation because of failure to paralyse or sedate patients fully, in order to rouse them for repeated neurological assessments. It is arguably wiser to accept about 48 h as the usual minimum time for which ventilatory control should be prescribed. The widely differing approaches to ventilatory therapy in different units perhaps explain why the pooled data from many centres show little benefit from such active therapy.

Frequent intensive care problems in severe head injuries are caused by hyponatraemia or hypernatraemia, but little guidance is provided on these topics.

Priorities in multiple injuries are sensibly discussed. Most neurosurgical anaesthetists would feel that it is essential that different surgical specialities co-ordinate their investigations and treatment so that the number and duration of anaesthetic procedures are minimized.

Less contentious chapters cover recovery and mental sequelae after head injury, including the higher risk group for late post-traumatic epilepsy.

The authors have tried hard to collate the predictive and prognostic factors in head injuries, but it is not yet possible to select the group of patients in whom active therapy will achieve dramatic results. Certainly children do so well that therapy seems to be worthwhile, but children do better than adults even in the most conservative units.

The Management of Head Injuries would have benefited from a contribution by an anaesthetist or intensive care expert in this field. Most head injuries are not treated by neurosurgeons and neuroanaesthetists, and therefore the doctors managing these patients are looking for guidance from both. Nevertheless, those chapters dealing with structural pathology, surgery, epidemiology and head injury planning are so excellent that the book merits a place in the library of every doctor who deals with head injuries.

R. Greenbaum

Non-invasive Cardiovascular Monitoring by Electrical Impedance Technique. By S. N. Mohapatra. Published (1981) by Pitman Medical. Pp. 282; illustrated; indexed. Price £26.00.

This monograph is a scholarly discourse on the theory and application of impedance cardiography and impedance plethysmography. It is a very comprehensive account, profusely illustrated and well referenced. The prospective physiologist, physicist or anaesthetist with a burning desire to conquer the complexities of the impedance cardiogram, either to measure stroke volume or to derive systolic time intervals, will find this book a valuable source of information. The sections on the origin of the impedance cardiogram, and on the derivation of stroke volume, are by no means unintelligible to those with a limited expertise in physics and electronics, and the author (a medical physicist) clearly has acquired a very adequate knowledge of the physiology and clinical application of his subject.

Emanating from the Research Department of Anaesthetics at the Royal College of Surgeons of England, this book has a greater association with anaesthesia than it might have done had the author been based in a Department of Cardiology or Medicine. What a pity, then, that few anaesthetists are likely to read, let alone buy, this book. After all, since Kubicek described the basis of impedance cardiography in 1966 and its application in aerospace medicine, fewer than 10 publications relate its use by anaesthetists or during anaesthesia. A book for reference rather than for reading in the operating theatre.

C. Prys-Roberts

Trends in Intravenous Anesthesia. Edited by J. Antonio Aldrete and Theodore H. Stanley. Published by Symposia Specialists Inc., Miami, U.S.A. Pp. 525; illustrated; indexed. Price £63.50.

The contents of this book have been compiled from the proceedings of the First International Symposium on Intravenous Anesthesia held in Denver in 1979. As is often the way with such volumes, some of its contents are out of date, there are areas of duplication from its variety of contributors, and it contains dissertations which, however elegant, are frankly irrelevant to the title. For instance, although interesting, the chapter on bioavailability and biotransformation concerns itself largely with orally taken drugs, and a chapter on thiopentone hardly represents a "trend"—even in 1979! Similarly the review of the actions of Althesin and propanidid would hardly seem to fit in with such a description.

The book commences with a chapter on the history and classification of i.v. anaesthetics by an acknowledged expert in this field, Professor Dundee from Belfast, who also contributes a chapter on the ideal i.v. anaesthetic, listing their "desirata"—a word that, along with the rather disjointed arrangement of several of the chapters, one suspects is the fault of the American editors. There are some interesting chapters on pharmacokinetics contributed by Kortilla and Keeri-Szanto (who present the idea, in a later chapter, of an MAC value for i.v. anaesthetics). Chapters on total i.v. techniques with etomidate and ketamine maintain the interest, while a touch of the unusual is added by a chapter with the intriguing title of "Procaine as Intravenous Anesthetic". This, however, proves to be somewhat misleading, as procaine is accompanied by a variety of other drugs in providing the anaesthesia. The newer i.v. compounds appear in the book at last with a chapter on midazolam from Belfast and the scope of the book at least is assured with chapters on placental transfer, the benzodiazepines, narcotics as complete anaesthetics, somnoanalgesia (which many have practised but didn't think it needed a name all to itself) and the universal antagonist. The book carries plenty of references, but I think the self-evaluation quizzes, in the style of multiple-choice questions, which follow each chapter will irritate many readers. There is also a section on adverse responses which, surprisingly in this field, fails to mention the problem of allergic reactions.

Because this book has been compiled from a collection of scientific papers the quality of its contents and thus the reader's interest fluctuates considerably, so it is not altogether a comfortable read. However, it is a useful reference book, although its price is a positive affront.

K. M. Rogers

OTHER BOOKS RECEIVED

An Introduction to Acupuncture: Treatment and Anesthesia. By M. Salim. Published by Ajaib Stores (Regd), Frere Road, Sukkur. Price Rs 50.

L'abord Vasculaire en Reanimation Chez l'Adulte. By Cl. Bouchard, J. Motin and J. H. Neidhardt. Published by SIMEP, 38–46 rue de Bruxelles, B.P. 1214, 69611 Villeurbanne Cedex, France. No price given.

This is a comprehensive volume describing the complete range of intravascular techniques of monitoring and resuscitation with a profusion of clearly presented anatomical drawings. The text, including the labelling of diagrams, is in French.

Precis d'Anesthesie. By G. Francois, M. Cara, J. Du Cailar, F. D'athis, F. Gouin and M. Poisvert. Published (1981) by Masson, Paris. Pp. 583; illustrated; indexed. No price given.

Functional Toxicity of Anaesthesia. By David L. Bruce. Published by Academic Press Inc. (London) Ltd. Pp. 125; illustrated; indexed. Price £8.80.

To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient. Edited by Leroy D. Vadam. Published by Addison-Wesley Publishing Co. Pp. 245; illustrated; indexed. Price $24.95.

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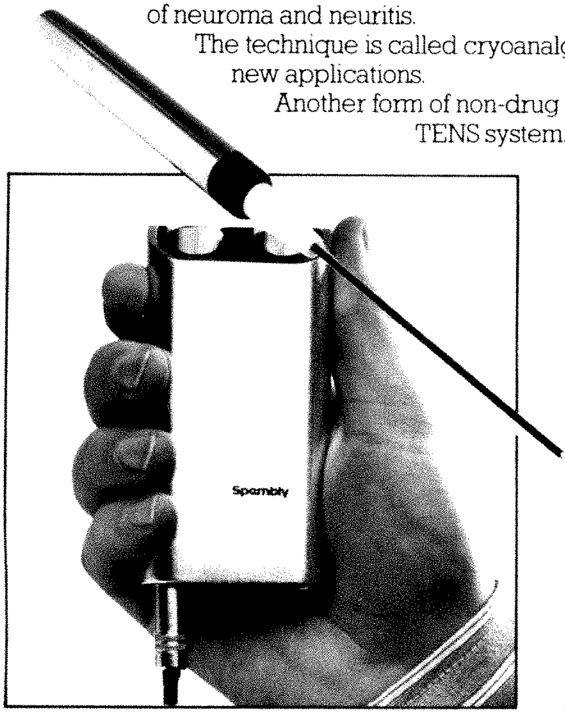

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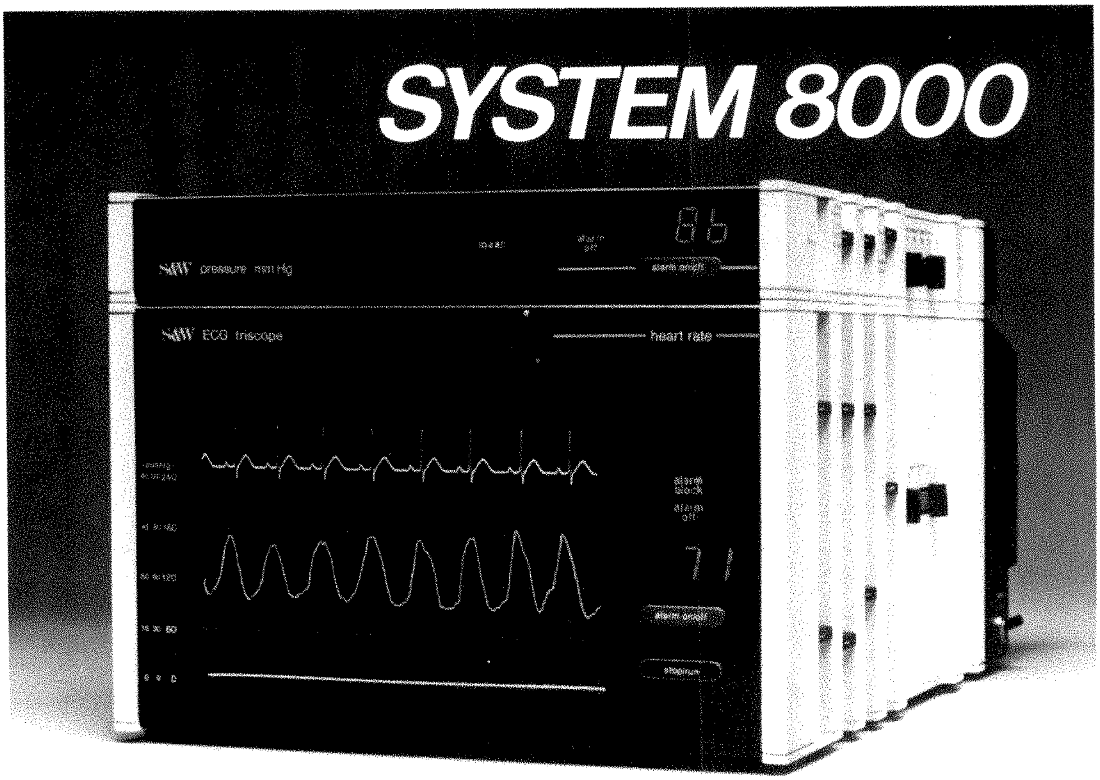

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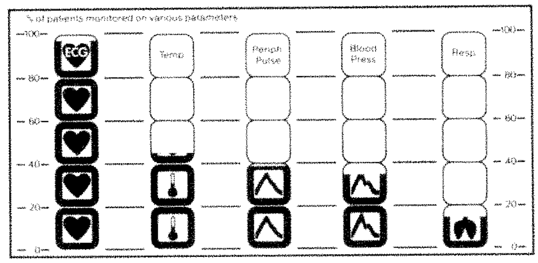

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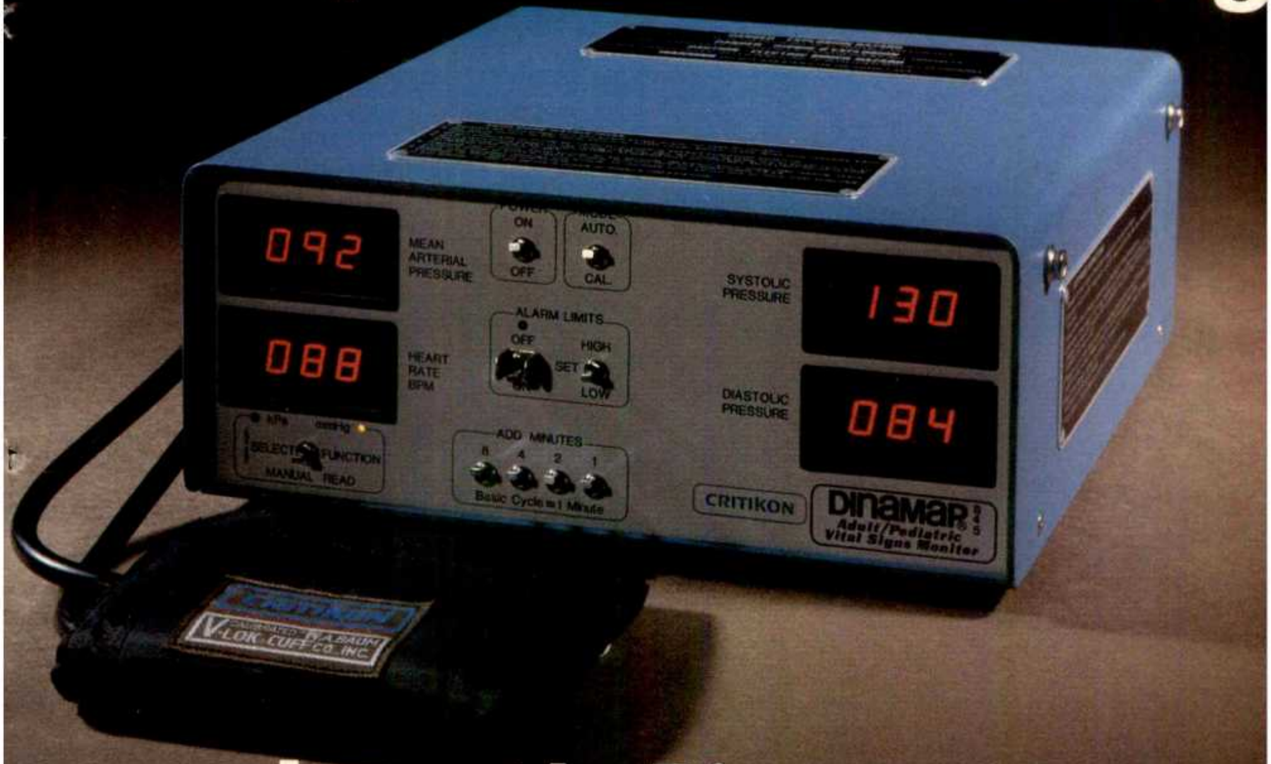

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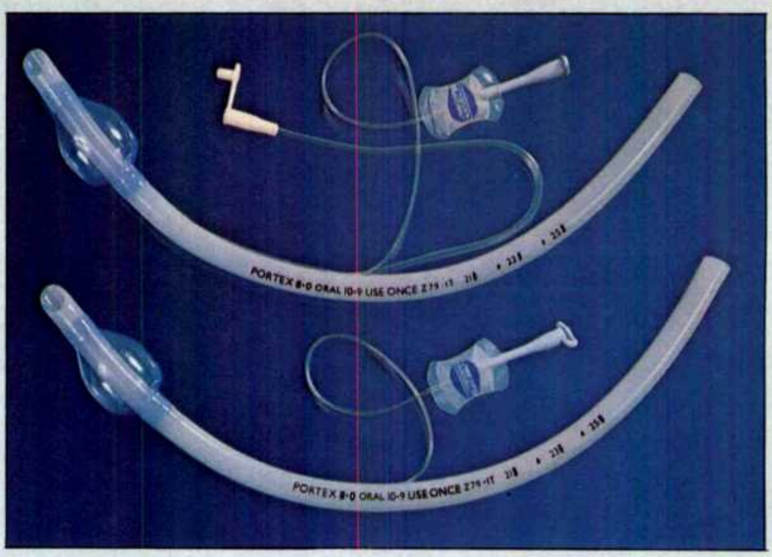

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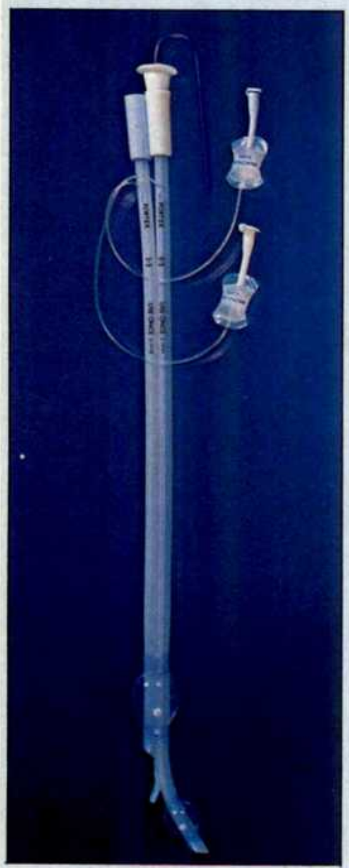

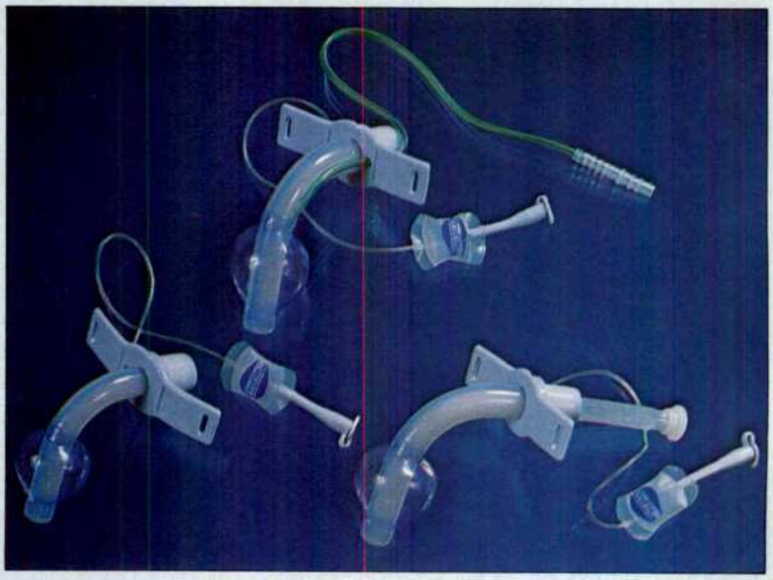

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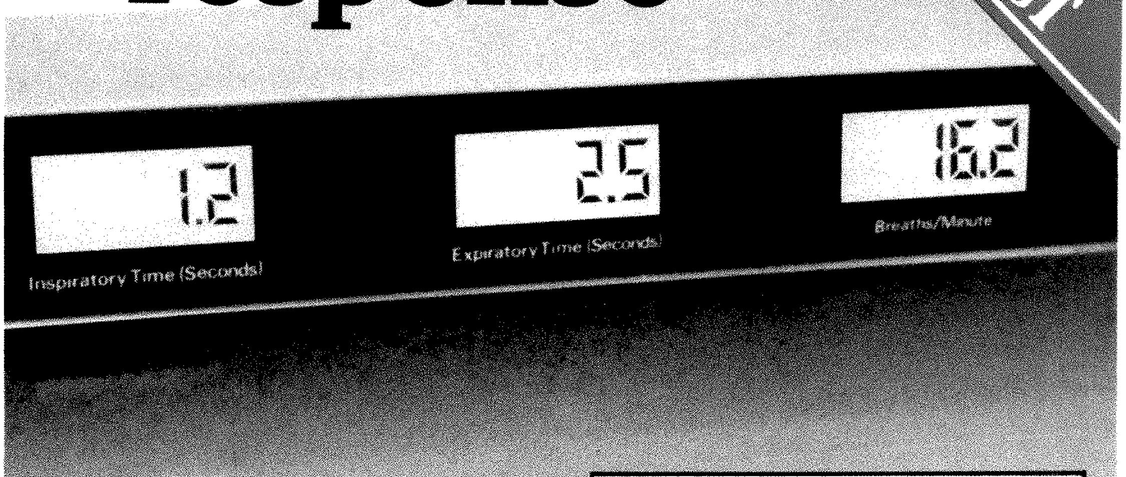

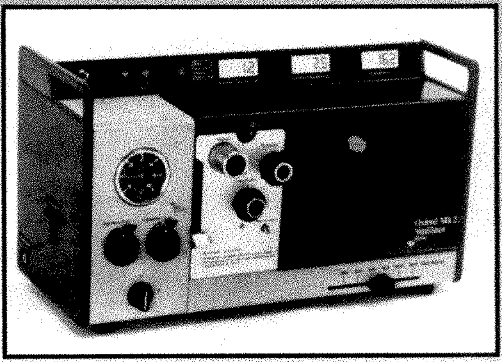

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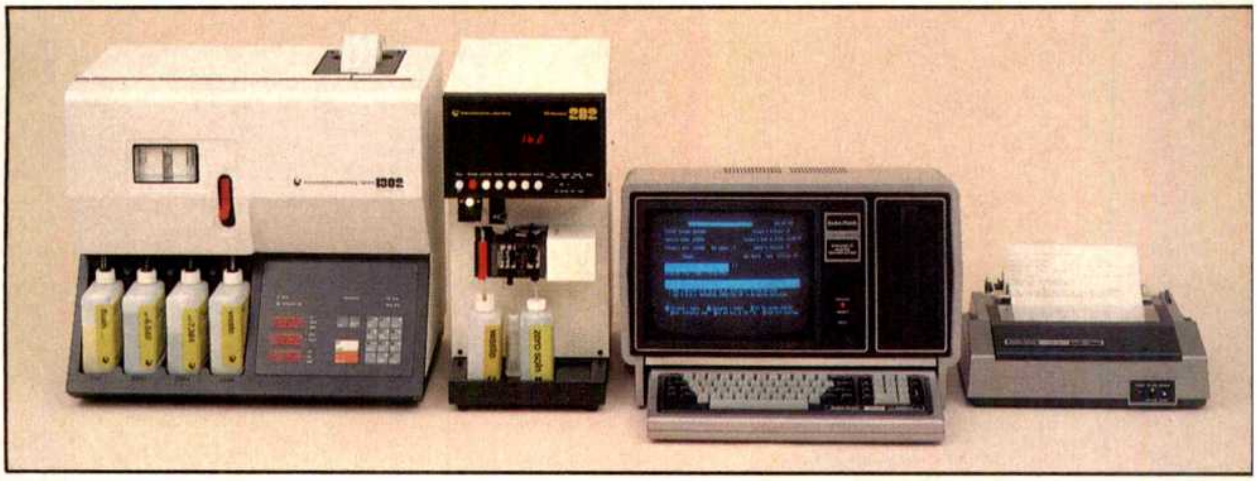

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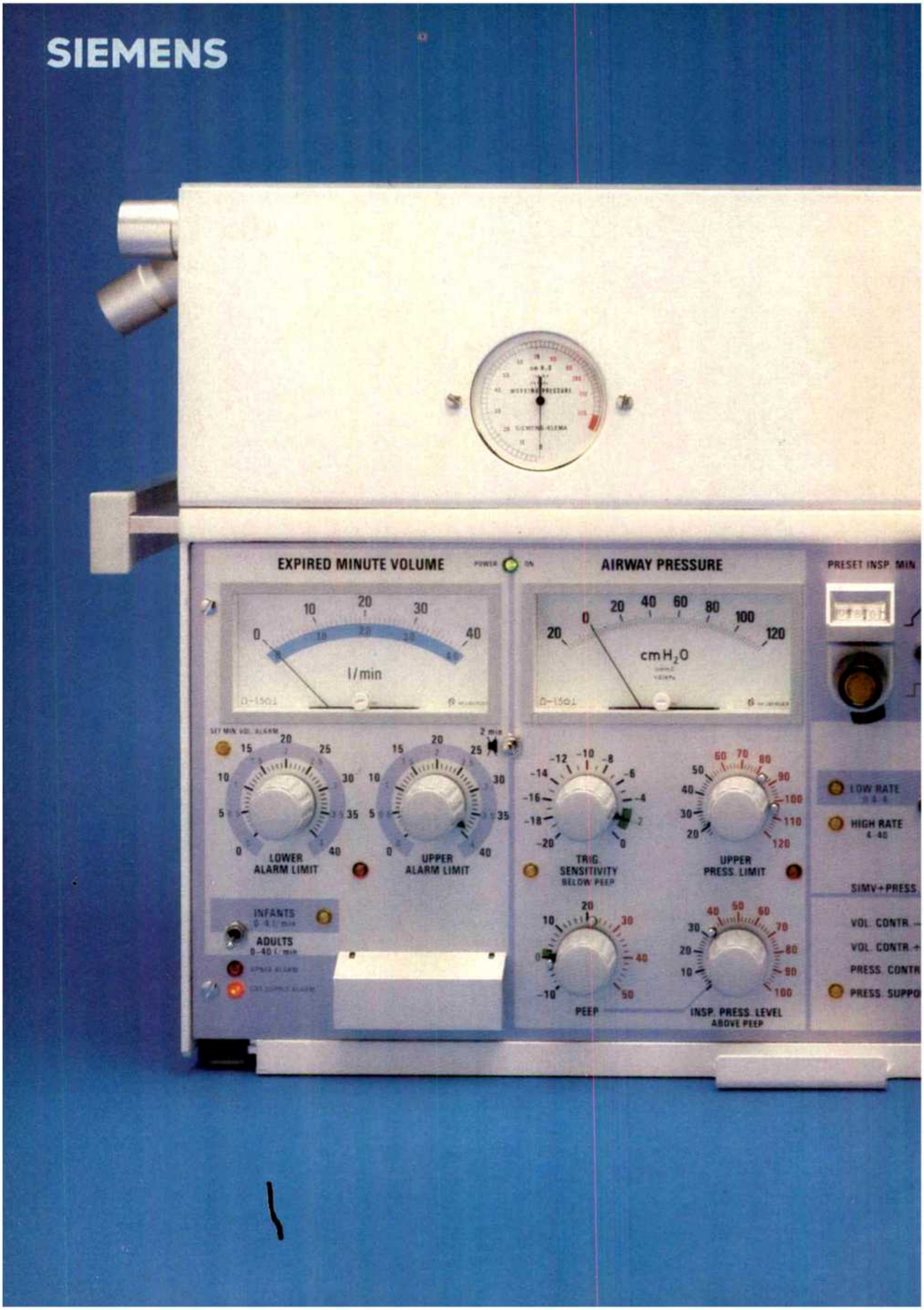
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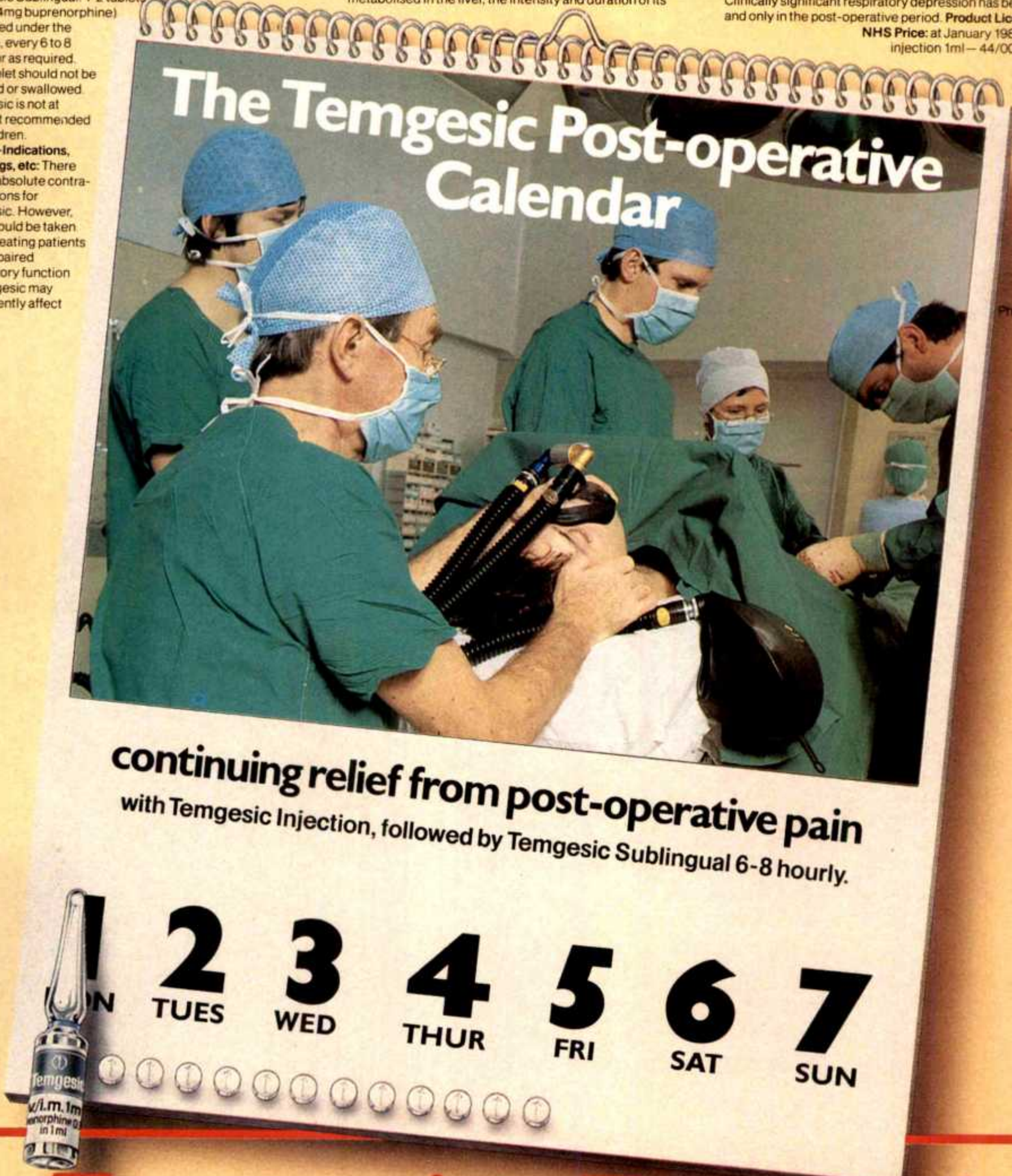
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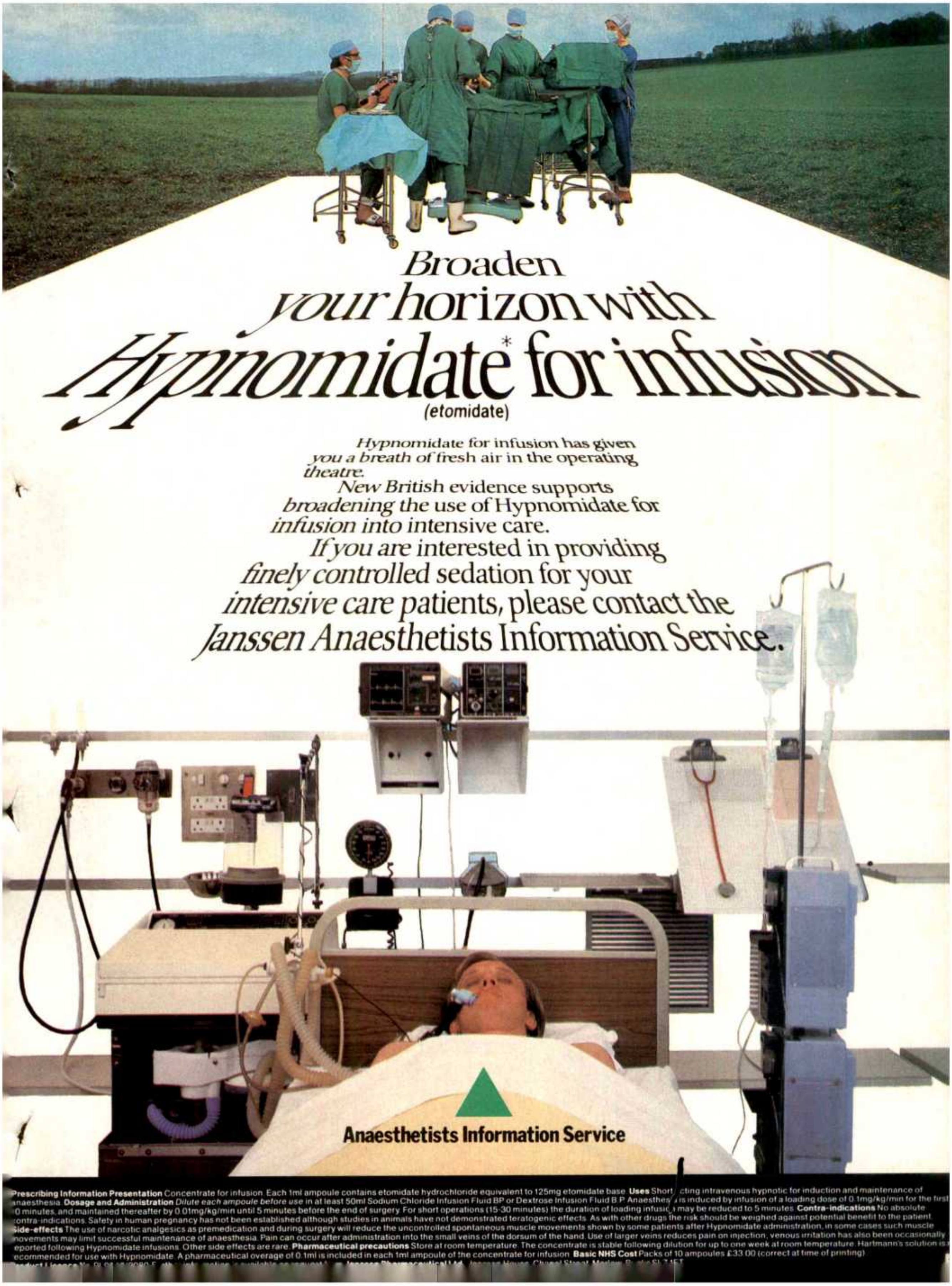

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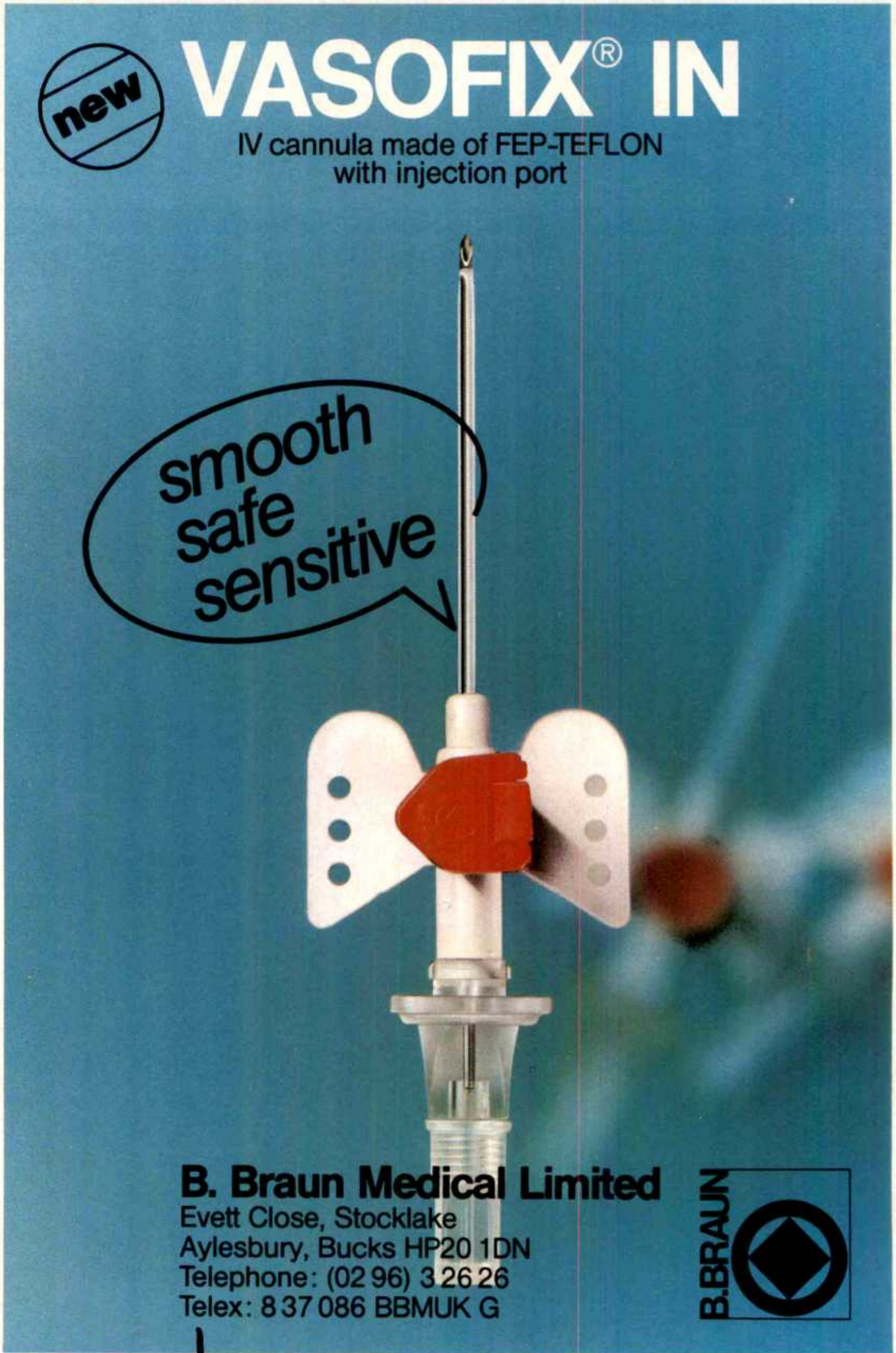

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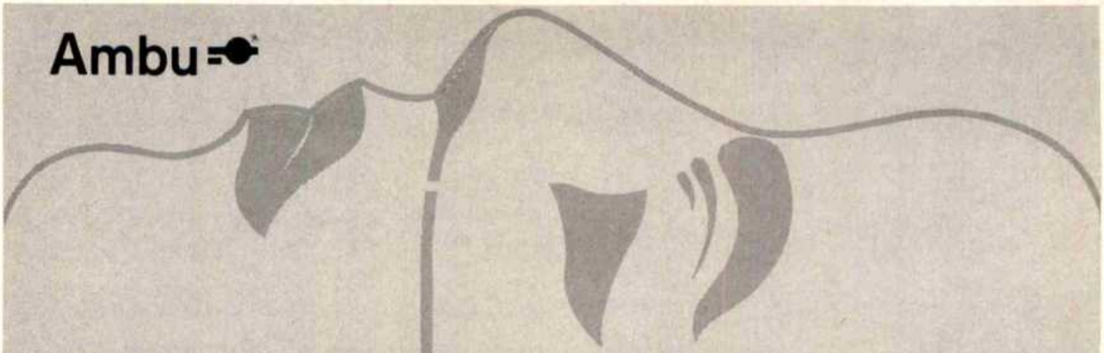

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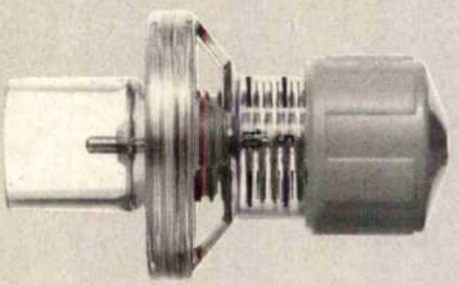

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W. L. M. BAIRD, W. C. BOWMAN AND W. J. KERR

SUMMARY

Some actions of the muscle relaxant drug Org NC45 on the tibialis anterior muscle of cats under barbiturate–chloralose anaesthesia have been studied. Its effects were characteristic of a neuromuscular blocking agent that acts predominantly, although not necessarily exclusively, by blocking postjunctional cholinoceptors. It was confirmed that one of the important features of the action of Org NC45 is that, despite its high potency, its offset of action is unusually rapid. The pronounced antagonism of the block following an interposed tetanus suggested that Org NC45 is more easily displaced from the endplate cholinoceptors than are tubocurarine or pancuronium, and this led to the idea, confirmed by experiment, that edrophonium would be a more effective antagonist of Org NC45 than of most other neuromuscular blocking drugs. Edrophonium was about 12 times less potent than neostigmine in antagonizing Org NC45. However, with equipotent antagonistic doses, edrophonium restored transmission to control (as measured by the train-of-four test) at least twice as rapidly as neostigmine and, more importantly, edrophonium had a much weaker effect than neostigmine on the cardiac vagus. The results obtained in cats with edrophonium were essentially confirmed in preliminary studies on nine anaesthetized patients. In these studies, a dose of edrophonium 0.5 mg kg^{-1} i.v. was found to produce adequate and rapid antagonism of Org NC45, and because of the relatively weak side-effects of edrophonium, it was necessary, about 30 s before edrophonium, to administer only 0.6 mg of atropine (about 9 μg kg^{-1}), which is half the dose commonly used when neostigmine is the reversal agent. These preliminary observations in man suggest that edrophonium may be the reversal agent of choice for Org NC45.

Org NC45 is the monoquaternary homologue of pancuronium in which the methyl group on the 2β nitrogen atom is lacking (Durant et al., 1979). Experiments on animals have shown it to be rapid in its offset of action, relatively non-cumulative and virtually free from the cardiovascular side-effects characteristic of most other neuromuscular blocking drugs (Durant et al., 1979; Booij, Edwards et al., 1980; Durant, Houwertjes and Crul, 1980). These advantages, demonstrable in animal experiments, have been confirmed in clinical trials on patients (Crul and Booij, 1980; Krieg, Crul and Booij, 1980; Agoston et al., 1980; Fahey et al., 1981), and Org NC45 therefore shows promise as a useful neuromuscular blocking drug of intermediate duration of action that is virtually free from side-effects. Much of the early work on Org NC45 was reported at a symposium, the proceedings of which have been published (Bowman and Norman, 1980). The experiments described in this paper were concerned with general aspects of the neuromuscular blocking action of Org NC45, but particular attention was paid to the antagonistic action of edrophonium.

METHODS

Cats

Cats of either sex were anaesthetized with a mixture of α-chloralose (80 mg kg^{-1} as a 1% solution in 0.9% sodium chloride solution) and sodium pentobarbitone (6 mg kg^{-1}) injected i.p. The trachea was intubated and positive pressure artificial ventilation was applied during periods of neuromuscular block.

The tendon of insertion of the tibialis anterior muscle of one limb was attached to a Grass (model FT 10C) force transducer after clamping the limb in a horizontal position by means of drills through the femur and the tibia and fibula. Muscle temperature was maintained at 36–38 °C by bathing the muscles in warm mineral oil (heavy liquid paraffin, B.P.) and warming with heat lamps. The animal was laid on an electrically heated blanket (Epil, Edinburgh). Muscle temperature was monitored from an adjacent muscle (extensor digitorum longus) by means of a temperature probe (Grant Instruments, Cambridge). The sciatic nerve was tightly ligated high in

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the popliteal space. Contractions of the tibialis anterior muscle were evoked by stimulating the trunk of the sciatic nerve, after sectioning the branches to other muscles. Rectangular pulses of 0.1 ms duration and of a strength about double that necessary to evoke a maximal twitch were applied from a Grass (model S4) stimulator and passed through a Grass (model SI5) stimulus isolation unit. Direct muscle stimulation, when required, was applied through a platinum wire inserted through the musculo–tendinous junction and an indifferent electrode attached to the drill in the femur. Rectangular pulses of 0.5 ms duration and of a strength such that the evoked contractions matched the indirectly-evoked maximal twitches were delivered from a second Grass (model S4) stimulator. The resting tension applied to the muscle was that giving the greatest evoked twitch tension. Arterial pressure was recorded by means of a Statham (model P23AC) pressure transducer connected to a common carotid artery. Heart rate was recorded by means of a Grass (model 7P4C) tachograph triggered by the arterial pulse. In eight experiments, the right vagus nerve in the neck was separated from the cervical sympathetic trunk and crushed centrally. The peripheral portion was stimulated through platinum hook electrodes at frequencies of 1–10 Hz for 10 s every 100 s. The responses to vagal stimulation were recorded as decreases in arterial pressure and in heart rate. The left vagus was severed in these experiments.

All records were made simultaneously on a Grass (model 7) polygraph.

In two cats, antidromic nerve action potentials in a ventral root were recorded simultaneously with the maximal twitches of the tibialis anterior muscle. In these experiments, the cats were laid prone on the operating table and the spinal cord was exposed from L6 to S1. All exposed ventral and dorsal roots were severed, and a ventral root that contained motor fibres to the tibialis anterior muscle was identified by stimulating it. The stimulating electrodes were then replaced by bipolar platinum recording electrodes so that the more central pole was in contact with the cut end of the root. The exposed cord and the recording electrodes were immersed in a pool of warm liquid paraffin formed by sewing the skin flaps to a metal collar. Twitches and antidromic nerve action potentials were then evoked by stimulating the sciatic nerve in the popliteal space as described above. The antidromic nerve action potentials were amplified by a Nihon Kohden Biophysical amplifier and displayed on a cathode ray oscilloscope (Nihon Kohden, model VC-7A) concurrently with the twitches which were recorded on the pen-recorder.

In two cats, the tibialis anterior muscle was prepared for close-arterial injection according to the method described by Brown (1938), and acetylcholine was injected close-arterially in a volume not exceeding 0.2 ml. I.v. injections and infusions were made through cannulae in the brachial veins, infusions being administered by means of a motorized syringe (Palmer) into the vein contralateral to that into which bolus injections were made.

Anaesthetized patients

Nine patients, all ascribed to categories 1 or 2 of the American Association of Anesthesiologists Classification of Fitness, were studied, informed consent having been obtained from each. Their ages ranged from 24 to 66 yr. Care was taken to ensure that they were not taking any concurrent drug therapy that might have interfered with the study.

Approximately 1 h after premedication with papaveretum, an initial dose of fentanyl 0.05–0.2 mg accompanied by droperidol 5–10 mg was given into an i.v. infusion. Anaesthesia was induced with a "sleep" dose of thiopentone (150–400 mg) followed immediately by suxamethonium 1 mg kg^{-1} to facilitate intubation. Anaesthesia was maintained with 70% nitrous oxide and oxygen with supplements of fentanyl 0.05–0.2 mg as required. Routine measurements of end-tidal carbon dioxide or blood-gas indices were not performed, but controlled ventilation was aimed at normocapnia, the respiratory rate and tidal volume being measured in the usual manner. The heart rate was recorded continuously from a Roche 105 ECG monitor, and arterial pressure was measured at regular intervals with a sphygmomanometer.

Supramaximal stimuli of 0.2 ms duration were applied at a frequency of 0.1 Hz from a Myotest peripheral nerve stimulator through needle electrodes placed close to the ulnar nerve at the wrist. The muscle twitch of the adductor pollicis muscle was recorded by means of an Ether UF1 force-displacement transducer connected to a Devices pre-amplifier and recorder unit. In addition, the train-of-four technique (Ali, Utting and Gray, 1971) was used to follow the recovery of neuromuscular blockade and its reversal.

Control values for twitch height and train-of-four were recorded and neuromuscular blockade was induced with Org NC 45.

RESULTS

Cats

Throughout the experiments Org NC45, in the doses used, was without effect on arterial pressure and heart rate and these records have been omitted from most of the figures. This demonstration of lack of cardiovascular side-effects confirms the much more detailed observations made by others (Durant et al., 1979; Durant, Houwertjes and Crul, 1980; Booij, Edwards et al., 1980; Marshall, McGrath et al., 1980).

In a dose of $35\,\mu g\,kg^{-1}$, Org NC45 produced 88 ± 4% block of the twitches of the tibialis anterior muscle evoked at a frequency of 0.1 Hz ($n = 10$). With the first dose, the time from injection to maximum twitch depression was 4.8 ± 0.4 min, which was not statistically significantly different ($P < 0.05$) from the onset of action of the first dose of pancuronium in this muscle (5.2 ± 0.5 min). The rate of recovery, measured as the time to recover from 25% to 75% of the control twitch amplitude (stimulation frequency 0.1 Hz) was 1.96 ± 0.2 min, which was two to three times as fast as the rate of recovery from pancuronium block (4.9 ± 0.9 min). The overall durations of the blocks (injection to 90% recovery) were 8.3 ± 1.2 min for Org NC45 and 14.3 ± 2 min for pancuronium. With the exception of the recovery rate from Org NC45, these results are in close agreement with those of Durant, Houwertjes and Crul (1980). We found the time to recover from 25% to 75% control twitch tension after Org NC45 to be substantially shorter than that reported by Durant, Houwertjes and Crul (1980) for the same muscle. We have no explanation to offer for this difference. The above comparisons with pancuronium are made with respect to initial doses of each drug. As others have also noted (Agoston et al., 1980; Durant, Houwertjes and Crul, 1980; Marshall, Agoston et al., 1980) cumulation between successive doses is much less with Org NC45 than with pancuronium, so that with repeated dosage the duration of action and time of recovery become relatively much longer with pancuronium.

During complete block of the twitches evoked by nerve stimulation, the antidromic nerve action potentials remained unaltered, and direct muscle stimulation evoked normal contractions (fig. 1). These observations located the site of action of Org NC45 specifically at the neuromuscular junction, since conduction in the motor axons and muscle contractility were clearly unaffected.

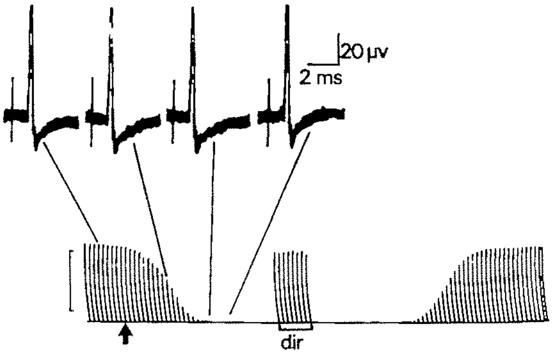

FIG. 1. Cat, chloralose anaesthesia. Maximal twitches of a tibialis anterior muscle and antidromic nerve action potentials recorded from a ventral root were evoked by stimulation of the motor nerve at a frequency of 0.1 Hz. The representative action potentials are associated with the twitches indicated by the oblique lines. At the arrow, Org NC45 $100\,\mu g\,kg^{-1}$ was injected i.v. This dose caused complete abolition of the twitches evoked by nerve stimulation, but was without effect on the nerve action potentials. During the block, the muscle responded normally to direct electrical stimulation (dir). Tension calibration = 5N.

During depression of the indirectly evoked twitches, contractions of the muscle produced by close-arterially injected acetylcholine 2–8 µg were blocked to a greater extent than were the twitches (fig. 2), indicating that the main action of Org NC45 is to block acetylcholine receptors rather than to impair acetylcholine release.

The depolarizing drugs suxamethonium, decamethonium, and carbolonium injected close-arterially in doses of 2–5 µg exerted some antagonistic action when injected during partial block produced by Org NC45 in the tibialis anterior muscle. In these experiments, partial block was maintained by a continuous infusion of Org NC45, so that antagonism would not be confused with spontaneous recovery. Figure 3 illustrates the antagonistic effect of suxamethonium. This type of antagonism

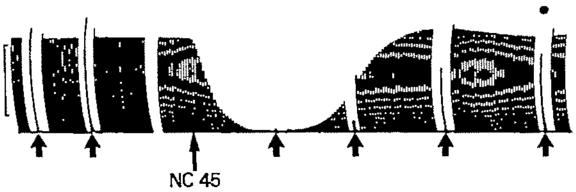

FIG. 2. Cat, chloralose anaesthesia. Maximal twitches of a tibialis anterior muscle were evoked by stimulation of the motor nerve at a frequency of 0.1 Hz. At intervals, electrical stimulation was temporarily stopped and acetylcholine 8µg was injected close-arterially into the muscle (unlabelled arrows). The contractions above the unlabelled arrows are the responses to acetylcholine. At NC45 Org NC45 $30\,\mu g\,kg^{-1}$ was injected i.v. During the block of the twitches evoked by nerve stimulation, the contractions produced by close-arterially injected acetylcholine were also blocked. Tension calibration = 5N.

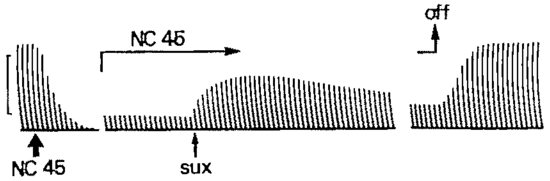

FIG. 3. Cat, chloralose anaesthesia. Maximal twitches of a tibialis anterior muscle were evoked by stimulation of the motor nerve at a frequency of 0.1 Hz. At NC45, a bolus injection of Org NC45 $50\,\mu g\,kg^{-1}$ was given (thick arrow). During the recovery from this dose, an i.v. infusion of Org NC45 was started and adjusted to give a constant partial block (NC45). The infusion was then maintained constant ($120\,\mu g\,kg^{-1}\,h^{-1}$) until the point indicated by "off". At sux, suxamethonium $5\,\mu g$ was injected close-arterially. Tension calibration = 5 N.

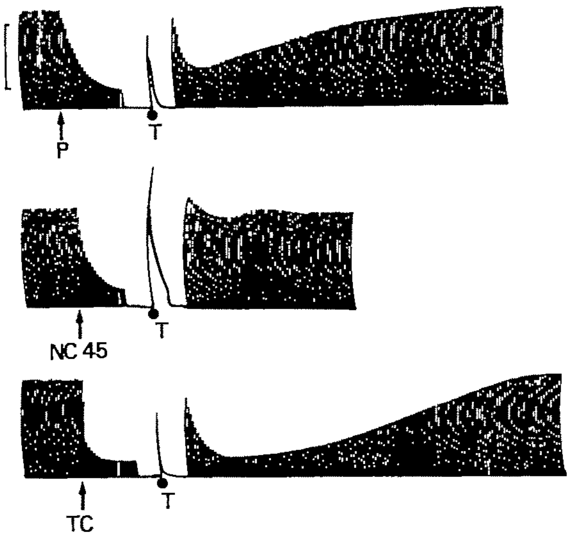

FIG. 4. Cat, chloralose anaesthesia. Maximal twitches of a tibialis anterior muscle were evoked by stimulation of the motor nerve at a frequency of 0.1 Hz. At P, pancuronium $20\mu g\,kg^{-1}$, at NC45, Org NC45 $35\mu g\,kg^{-1}$, and at TC, tubocurarine $300\mu g\,kg^{-1}$ were injected. About 4.5 min after injection, during the partial blocks produced, a tetanus (T) (100 Hz for 10 s) was interposed. The paper speed was increased during the tetani. The duration of tetanic stimulation in each case is indicated by the tetanus evoked during Org NC45 block, since tetanic fade in this instance was less than complete. Tetanic fade was least and post-tetanic antagonism was greatest during Org NC45 block. In these respects, pancuronium came next and tubocurarine last. At least 3 h elapsed between the effects of the injections illustrated. (Two smaller doses of Org NC45 and three smaller doses of tubocurarine (effects not shown) had been injected before each of the illustrated blocks produced by these drugs. These omitted doses were administered in unsuccessful attempts to match the pancuronium block.) Tension calibration = 5 N.

of a non-depolarizing blocking drug by a depolarizing blocking drug was first demonstrated with tubocurarine and decamethonium (Paton and Zaimis, 1952).

During partial twitch block produced by a non-depolarizing neuromuscular blocking drug tetanic tension is depressed in amplitude and is non-sustained (tetanic fade); the post-tetanic facilitation of transmission results in some degree of antagonism of the block (Paton and Zaimis, 1952). Org NC45 qualitatively behaved like other non-depolarizing neuromuscular blocking drugs in this respect. However, at a given degree of twitch block, the amplitude of an interposed tetanus seemed greater and the post-tetanic relief of the block appeared more pronounced than experience suggested was the case with other blocking drugs of this type. This impression prompted a comparative study of Org NC45 with tubocurarine and pancuronium in which the conditions (duration and frequency of tetanus, time of application of tetanus after injection, degree of twitch block during which tetanus applied) were made as comparable as possible in each cat. The results confirmed the earlier impression, and a representative experiment is illustrated in figure 4. In this experiment a tetanus (100 Hz for 10 s) was interposed 4–5 min after injection of pancuronium, Org NC45 or tubocurarine at a time when the twitches were about 85% depressed. In another experiment the same pattern was followed, and in two further experiments Org NC45 was injected first, followed by pancuronium and tubocurarine. The degree of tetanic fade and the extent and duration of the post-tetanic relief of the block varied from experiment to experiment, but the trend illustrated in figure 4 was consistent. That is, tetanic fade was greatest and post-tetanic relief of the block least, and shortest in duration, with tubocurarine. The other extreme was exhibited by Org NC45, tetanic fade being least and post-tetanic relief of the block greatest with this drug. Pancuronium held an intermediate position between the other two drugs. With Org NC45, the post-tetanic twitches were often restored almost to control (as in figure 4), and block was not reinstated.

The relatively rapid recovery from Org NC45, coupled with the pronounced antagonism produced by a tetanus suggested that the block produced by this drug is more labile than that produced by pancuronium or tubocurarine. This may be interpreted to mean that molecules of Org NC45 are more readily displaced from the junctional cholinoceptors than are molecules of pancuronium or tubocurarine.

The antagonistic actions of neostigmine and pyridostigmine against Org NC45 are pronounced and have been well documented (Booij, van de Pol et al., 1980; Durant, Houwertjes and Crul, 1980). Edrophonium is generally considered to be too short-acting for use as a reliable reversal agent against block produced by non-depolarizing neuromuscular blocking drugs. However, the idea that the block produced by Org NC45 is more labile than that produced by most other blocking drugs, led us to compare the antagonistic actions of edrophonium against it, with that against pancuronium and tubocurarine.

In a dose of 0.25 mg kg^{-1} i.v., edrophonium produced rapid, apparently complete, and permanent antagonism of 90–100% tibialis anterior twitch block produced by Org NC45 in four cats. When the same dose was administered during similar depths of block produced in different experiments by tubocurarine or pancuronium, the antagonism was less complete and some reinstatement of the block usually occurred. The degrees of antagonism against tubocurarine and pancuronium were somewhat variable from experiment to experiment but, as with the effects of a tetanus, it was clear that the antagonistic effect of edrophonium was greatest and longest lasting against Org NC45, as illustrated in figure 5.

These results showed that edrophonium was more active against Org NC45 than against pancuronium and tubocurarine, but they did not give an indication of the dose necessary for full antagonism. Train-of-four stimulation (2 Hz for 2 s) (Ali, Utting and Gray, 1971) allows a better estimate of the effective antagonist dose, and for this reason train-of-four stimulation was interposed at convenient times in the series of twitches evoked at 0.1 Hz. Figure 5 illustrates typical experiments. Although, as already mentioned, during block produced by Org NC45, edrophonium 0.25 mg kg^{-1} rapidly restored twitches evoked at a frequency of 0.1 Hz to control amplitude, train-of-four stimulation showed that a residual block persisted for a further 4–6 min (fig. 5A). As would be expected, train-of-four recovery was considerably slower with pancuronium (fig. 5B), and was slowest of all with tubocurarine (fig. 5C). In a further four experiments, Org NC45 was the only drug used to produce neuromuscular block. These experiments showed that when the dose of edrophonium was increased to 0.5 or 0.75 mg kg^{-1}, no significant train-of-four fade was detectable from the moment that the "single" twitches reached con-

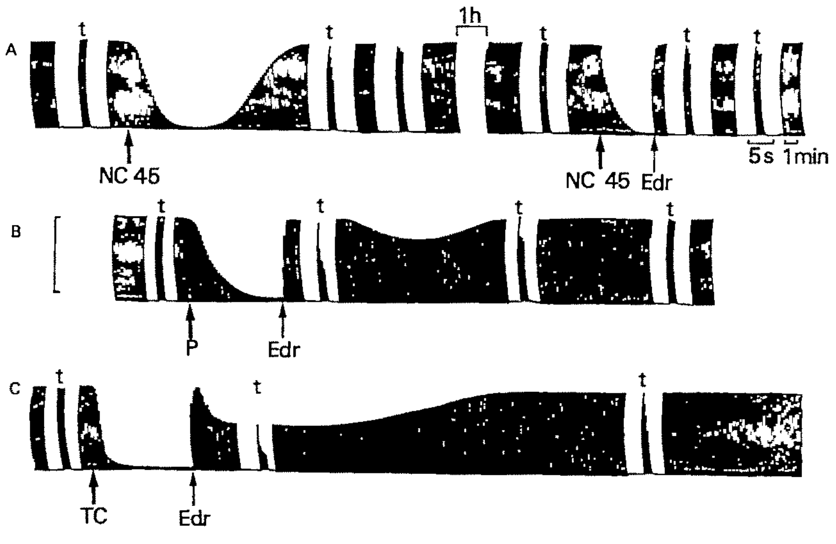

FIG. 5. Cats, chloralose anaesthesia. A, B and C are from different experiments. Maximal twitches of tibialis anterior muscles were evoked by stimulation of the motor nerves at a frequency of 0.1 Hz, but train-of-four stimulation (2 Hz for 2 s) was interposed where appropriate (t). At NC45, Org NC45 40 μg kg^{-1}, at P, pancuronium 22 μg kg^{-1} and at TC, tubocurarine 400 μg kg^{-1} were injected. At Edr, edrophonium 0.25 mg kg^{-1} was injected. This dose of edrophonium completely restored the twitches blocked by Org NC45 to control, but the responses to train-of-four stimulation were 3–4 min slower to recover to control amplitude than were the responses to single-shock (0.1 Hz) stimulation. The antagonistic action of this dose of edrophonium was clearly less against pancuronium and tubocurarine than against Org NC45. Tension calibration = 5 N.

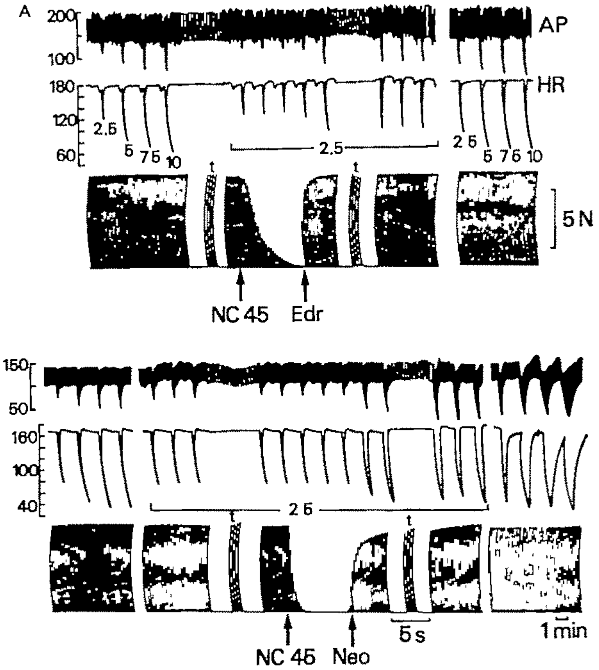

FIG. 6. Cats, chloralose anaesthesia. A and B are from different experiments. Maximal twitches of tibialis anterior muscles were elicited by stimulation of the motor nerves at a frequency of 0.1 Hz and train-of-four stimulation (2 Hz for 2 s) was interposed where appropriate (t). The upper records in each panel are arterial pressure (AP) and heart rate (HR). Bradycardia and depressor responses were evoked every 100 s by stimulation of the right vagus. The left and right ends of A and B show frequency-response relationships to vagal stimulation, the frequency (Hz) being indicated below each response in A. In the centre portions, the frequency was constant at 2.5 Hz. At NC45 in both A and B, Org NC45 40 μg kg^{-1} was injected. At Edr, edrophonium 0.6 mg kg^{-1} and at Neo, neostigmine 50 μg kg^{-1} were injected. With these doses, responses to train-of-four stimulation had fully recovered by the time the single twitches (0.1 Hz) returned to control. Both anticholinesterase drugs increased the responses to vagal stimulation, but only neostigmine produced clear prolongation of the responses. Atropine was not administered to these cats.

trol amplitude (60–80 s after injection of edrophonium). This rapid and complete antagonism produced by edrophonium is evident in the muscle record of figure 6A.

In a further series of eight experiments, arterial pressure, heart rate and muscle contractions were recorded simultaneously, and the right vagus nerve was stimulated at intervals to produce bradycardia and hypotension. The antagonistic actions of edrophonium 0.6 mg kg^{-1} were compared with those of neostigmine 0.04–0.07 mg kg^{-1} against Org NC45 although, since the one modified the effects of the other, it was not possible to study both antagonists meaningfully in the same cat. The results showed that neostigmine 0.05 mg kg^{-1} (fig. 6B) was about equiactive with edrophonium 0.6 mg kg^{-1} (fig. 6A) in antagonizing Org NC45 block to the extent that no train-of-four fade was evident as soon as the twitches (evoked at 0.1 Hz) reached control amplitude. That is, neostigmine was approximately 12 times more potent than edrophonium in antagonizing Org NC45. However, in confirmation of the results of other workers (Wescoe and Riker, 1951; Katz, 1967), edrophonium produced full antagonism more than twice as rapidly as did neostigmine (fig. 6). In eight experiments with edrophonium, full recovery of the twitch occurred within 60–90 s after injection, whereas in four experiments with neostigmine, the same degree of antagonism took from 150 to 220 s after injection.

No atropine was given in these experiments in order that the effects of edrophonium and neostigmine on heart rate and arterial pressure could be examined. Since both vagi were severed, neither of the anticholinesterase agents had much effect on resting heart rate. Their effects were studied against a background of intermittent vagal stimulation as described in Methods. Either a fixed submaximal frequency of vagal stimulation was applied intermittently throughout (e.g. 2.5 Hz for 10 s every 100 s), or a range of ascending frequencies (e.g. 2.5, 5, 7.5, 10 Hz each for 10 s every 100 s) was applied at the beginning and the end, with a fixed submaximal frequency applied intermittently between. The procedure of such an experiment is illustrated by figure 6.

Both edrophonium 0.6 mg kg^{-1} and neostigmine 0.05 mg kg^{-1} increased the extent of the bradycardia, and consequent hypotension, produced by vagal stimulation. Both also prolonged the individual responses to vagal stimulation in that the heart rate was slower to return to control when the stimulation was stopped. However, in this respect a difference was evident between the effects of edrophonium and neostigmine, the prolongation produced by neostigmine being considerably greater than that produced by edrophonium as illustrated in figure 6. A further difference between the two antagonists was evident in the overall durations of the cardiovascular effects, although these were not easy to measure with accuracy owing to the difficulty of determining the exact times when the responses to vagal stimulation had returned to the control amplitudes. Nevertheless, it was clear that the effects of edrophonium on the cardiac vagus disappeared in less than 1 h, whereas the effects of neostigmine were still evident after 2 h.

The results obtained in the cat experiments suggested that because of the lability of the block produced by Org NC 45, edrophonium might be an effective antagonist in man. For this reason, preliminary observations with edrophonium were made in a small group of human patients in whom muscle relaxation during surgery was produced by Org NC 45.

Clinical studies

The animal experiments suggested that a dose of edrophonium 0.5–1 mg kg^{-1} might be a fully effective antagonistic dose against Org NC 45. Furthermore, while this work was in progress, doses of this magnitude were reported to be effective antagonists of pancuronium (Bevan, 1979; Kopman, 1979; Ferguson, Egerszegi and Bevan, 1980). In preliminary human studies, we found doses up to 0.2 mg kg^{-1} to be incompletely effective against Org NC 45. It was therefore decided to assess the effects of 0.5 mg kg^{-1} and 1 mg kg^{-1} administered when spontaneous recovery of the adductor pollicis twitch had reached a level of about 25%. Figure 7 illustrates typical results recorded from two patients. In one (fig. 7A), an initial dose (0.1 mg kg^{-1}) followed by two maintenance doses (0.025 mg kg^{-1}) of Org

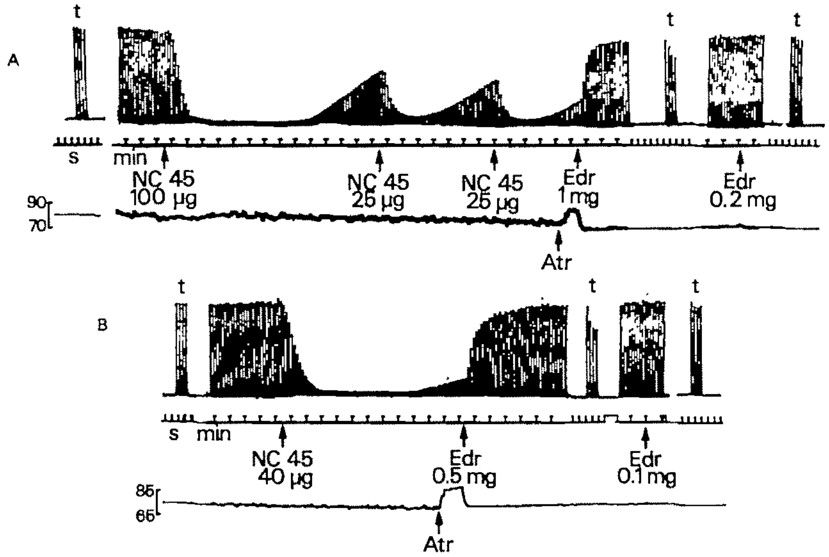

FIG. 7. Human patients. A and B are from studies on different individuals. Upper traces: flexions of the thumb in response to ulnar nerve stimulation; t = train-of-four, remaining contractions in response to stimulation at 0.1 Hz. Middle traces: time trace (s) for train-of-four, and (min) for remaining contractions. Lower traces: heart rate calibrated in beat min^{-1}. At NC 45, Org NC 45 and at Edr, edrophonium injected i.v. The doses shown are the amounts per kg body weight. At Atr, atropine 0.6 mg per patient was injected.

NC 45 were administered. Atropine (0.6 mg; about 0.01 mg kg^{-1}) was injected about 90 s before edrophonium; it produced a small increase in heart rate which was quickly restored to the control rate on injection of the edrophonium.

In a dose of 0.5 mg kg^{-1}, edrophonium rapidly restored the twitches of the adductor pollicis to 90% of control within 70–100 s. Full recovery to control took a further 2–4 min. With the larger dose of 1 mg kg^{-1}, the rate of antagonism was quicker, 90% of control being reached in 40–60 s, and full recovery in a further 1.5–2 min. Even at the time of full recovery of twitches (0.1 Hz) the train-of-four ratio (the last twitch as a percentage of the first) was only 75–84%, and although this correlates with the clinical signs of adequate recovery from non-depolarizing block (Ali and Kitz, 1973), attempts were made to restore the ratio to 100% by administering supplementary doses of edrophonium 0.1–0.2 mg kg^{-1}. Such supplementary doses (fig. 7) did not affect the twitches evoked at 0.1 Hz, but the train-of-four ratio was then restored to control (more than 95%). However, the total time elapsing from the point at which edrophonium had been first administered (at about 25% twitch tension) to a normal train-of-four ratio (>95%) was of the order of 6–8 min, by which time spontaneous recovery would probably have accounted for restoration of normal function. It thus appeared that edrophonium, in a dose of 0.5–1.0 mg kg^{-1}, produced a rapid restoration of neuromuscular function to around 80% of control as measured by the train-of-four test, but that no further benefit over that occurring spontaneously could be gained by supplementary doses.

DISCUSSION

The results show that, in the cat, Org NC 45 exhibits the characteristics typical of a non-depolarizing neuromuscular blocking drug, the primary action of which is to block post-junctional motor endplate cholinoceptors. Thus, in neuromuscular blocking doses, the response to injected acetylcholine is abolished, but conduction in the motor axons remains unaffected and the muscle still responds to direct electrical stimulation. Like other drugs in the same group, the neuromuscular blocking action is antagonized by depolarizing drugs (suxamethonium, decamethonium, carbolonium), by edrophonium, and following a tetanus: tetanic tension is characteristically poorly sustained. To these characteristics, antagonism by other anticholinesterases and by aminopyridines (Booij, van der Pol et al., 1980; Durant, Houwertjes and Crul, 1980; Marshall, Agoston et al., 1980) may be added the observation that Org NC 45 blocks the muscle responses to injected acetylcholine in neuromuscular blocking doses does not of course exclude the possibility that the drug also acts on motor nerve endings, but it demonstrates that the main site of action is postjunctional.

The potency of Org NC 45 and the time-course of its blocking action noted in the cat tibialis anterior muscle and in man, essentially agree with the results of other workers who studied the same species (cat: Durant et al., 1979; Durant, Houwertjes and Crul, 1980; Marshall, Agoston et al., 1980; man: Agoston et al., 1980; Krieg, Crul and Booij, 1980; Fahey et al., 1981). In general, throughout the species, including man, Org NC 45 is of the same order of potency as pancuronium with a comparable rate of onset of action. It differs from pancuronium, however, in its shorter duration of action, more rapid rate of recovery and relative lack of cumulative effects. It is also much less liable to produce cardiovascular side-effects, and on the whole these properties give it distinct advantages.

Results in the cat in which a tetanus was applied or edrophonium administered indicated that the block produced by Org NC 45 is more labile than that produced by pancuronium or tubocurarine. The binding of Org NC 45 to the junctional cholinoceptors thus appears to be less firm, perhaps partly because the type of co-operative chemical degradation envisaged by Savage (1980) occurs in the junctional cleft. It is possible that, as molecules are displaced from the endplate cholinoceptors in the junctional cleft, their rebinding to the receptors is prevented because, in the locally high concentration, they are chemically inactivated through a so-called neighbouring group effect in which the tertiary basic 2 β-nitrogen facilitates the conversion of the 3- and the 17-acetoxy groups to hydroxyl functions (Savage, 1980). Whatever the explanation of the easy reversal of the block, the results indicated that a study of antagonism by edrophonium might be worthwhile. Edrophonium has been regarded as having too short a duration of action to be reliable as a reversal agent, but this opinion was based on observations in which tubocurarine was the neuromuscular blocking drug used (see for example, Katz, 1967). Tubocurarine not only produces a considerably longer lasting block than Org NC 45, but it is also much more cumulative in its effects, so that reinstatement of its blocking action is more likely. Results of the cat experiments indicated that edrophonium does antagonize Org NC 45 more reliably than it antagonizes tubocurarine or pancuronium.

Comparison with neostigmine showed edrophonium to be about 12 times less potent, and indicated a dose of edrophonium 0.5–1.0 mg kg^{-1} to be a reliable antagonistic dose of Org NC45. This dose is bigger than has been commonly tested in the past, although in more recent studies in man (Bevan, 1979; Kopman, 1979; Ferguson, Egerszegi and Bevan, 1980) doses up to this magnitude were used effectively against pancuronium. Morris and others (1981) have recently reported that the pharmacokinetic behaviour of such large doses in man is essentially similar to that of equiactive reversing doses of neostigmine. The question then arises as to whether there is any advantage to be gained, other than a more rapid antagonism, in using a large dose of edrophonium instead of the usual dose of neostigmine. The animal experiments suggested that there might indeed be additional advantages. In the animal experiments, atropine was deliberately not used so that the effects of edrophonium and neostigmine on the activity of the cardiac vagus could be compared. Both anticholinesterase drugs potentiated vagal activity, but there was a clear difference between the effects of the two drugs. Not only did the effect of neostigmine on the cardiac vagus last longer in overall terms but, more importantly, its potentiating effect on the individual vagal bursts of activity was greater than that of edrophonium. It is not obvious why the effects of each burst of vagal stimulation should be less prolonged by edrophonium than by neostigmine, even at equal degrees of potentiation, but it might be explicable in terms of a more dynamic interaction between edrophonium and cholinesterase molecules. Thus, if edrophonium molecules repetitively combine with and are released from cholinesterase even at the height of their inhibitory effect, some hydrolysis of the vagally released acetylcholine will be permitted to occur during the periods when the enzyme molecules are free from the inhibitor, and thus the effects of each vagal volley will be less persistent than with an inhibitor which remains in combination with the enzyme. An additional factor that should possibly be taken into account is that equal degrees of neuromuscular facilitation, and similarity in pharmacokinetic profile, do not necessarily mean equal degrees of acetylcholinesterase inhibition. There has long been a suggestion that at least part of the facilitatory action of edrophonium on neuromuscular transmission is independent of cholinesterase inhibition (for example, Blaber, 1972; Riker, 1975; Lee, Yang and Katz, 1978). If this is so, then for equal degrees of antagonism of Org NC45, neostigmine may produce more cholinesterase inhibition than edrophonium and thus give rise to more pronounced autonomic effects.

Whatever the reason for the weaker effects of edrophonium on the cardiac vagus, the results in the cat suggested that less atropine might be needed to prevent its muscarinic effects in man. Preliminary results on human patients supported this suggestion. An adequate dose of edrophonium to antagonize Org NC45 in man was found to be 0.5 mg kg^{-1}, which is essentially the same as in the cat, and the cardiac effects of this dose of edrophonium were completely prevented by a single bolus dose of atropine sulphate 0.6 mg. This dose of atropine is half of that routinely given in the Glasgow Royal Infirmary to prevent the muscarinic effects of neostigmine. Since the effects of edrophonium are so rapid in onset, it seems preferable, as recommended by Bevan (1979), that the injection of atropine should precede that of edrophonium by 30–60 s.

These preliminary results in man suggest that edrophonium in a bolus dose of 0.5 mg kg^{-1} is a particularly effective antagonist of Org NC45, because spontaneous recovery from this blocking drug is in any case normally rapid, and cumulation is minimal. Edrophonium may in fact be the preferred reversal agent for routine use with Org NC45, having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug. If it is additionally shown that the muscarinic effects of edrophonium on the gut are, like its effects on the heart, also less than those of neostigmine, then a further advantage might be that the complications ascribed to neostigmine following ileorectal anastomosis (Bell and Lewis, 1968; Wilkins et al., 1970) might be avoided. Further experiments will be directed to comparing the effects on the gut of equiactive neuromuscular doses of edrophonium and neostigmine.

At the same time it should be pointed out that where atropine or an anticholinesterase drug is contraindicated, spontaneous recovery from Org NC45 may be rapid enough to permit their omission with safety. Obviously, a decision to forego the use of a reversal agent could be made only on the basis of continuous monitoring of the degree of block by means of a peripheral nerve stimulator.

Note added in proof: Two recent abstracts add support to the conclusions put forward in this paper. Foldes and colleagues have obtained essentially the same results in a larger series of patients, and Morris and colleagues have shown that the dose of atropine required to prevent muscarinic effects is smaller for edrophonium than for neostigmine (see, respectively, *Anesthesiology* (1981), 55, A201 and A206).

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QUELQUES EFFETS DE L'ORG NC45 ET DE L'EDROPHONIUM CHEZ LE CHAT ANESTHESIE ET CHEZ L'HOMME

RESUME

Nous avons étudié quelques effets de l'agent myorelaxant Org NC45 sur le muscle tibial antérieur de chats anesthésiés au barbiturique–chloral. Ses effets sont caractéristiques d'un agent bloquant la transmission neuromusculaire par une action prédominante, bien que pas nécessairement exclusive, sur les récepteurs post-synaptiques à l'acétylcholine. Nous avons confirmé que l'une des caractéristiques importantes de l'action de l'Org NC45 est que, malgré sa grande puissance, cette action est d'une durée inhabituellement brève. L'antagonisme marqué du bloc après interposition d'un tétanos suggère que l'Org NC45 est plus facilement déplacé des récepteurs post-synaptiques à l'acétylcholine que la tubocurarine ou le pancuronium, et ceci a conduit à l'idée confirmée expérimentalement, que l'édrophonium serait un antagoniste plus efficace de l'Org NC45 que la plupart des autres agents qui bloquent la jonction neuromusculaire. L'édrophonium s'est montré environ 12 fois moins puissant que la néostigmine pour antagoniser l'Org NC45. Cependant, à des

doses d'antagnonistes équipotentes, l'édrophonium a rétabli la transmission à son niveau initial (mesuré par le test du train de quatre) au moins deux fois plus vite que la néostigmine, et, ce qui est plus important, l'effet de l'édrophonium sur le parasympathique cardiaque s'est révélé bien moindre que celui de la néostigmine. Les résultats obtenus chez des chats avec l'édrophonium ont été, pour l'essentiel, confirmés dans des études préliminaires faîtes chez neuf patients anesthésiés. Dans ces études, on a montré qu'une dose de 0.5 mg kg^{-1} d'édrophonium entraînait une annulation correcte et rapide des effets de l'Org NC 45, et, grâce aux effets secondaires relativement faibles de l'édrophonium, il était suffisant d'injecter, environ 30 s avant l'édrophonium, 0,6 mg d'atropine (soit 9 μg kg^{-1}), ce qui est la moitié de la dose habituellement utilisée lorsqu' on utilise la néostigmine pour annuler le bloc. Ces études préliminaires chez l'homme suggèrent que l'édrophonium pourrait bien être l'antagoniste de choix de l'Org NC 45.

EINIGE WIRKUNGEN VON ORG NC45 UND VON EDROPHONIUM AN DER NARKOTISIERTEN KATZE UND BEIM MENSCHEN

ZUSAMMENFASSUNG

Einige Wirkungen des Muskelrelaxans Org NC45 am M. tibialis anterior von Katzen unter Barbiturat- oder Chloralose-Narkose wurden untersucht. Seine Wirkungen waren charakteristisch für einen neuromuskulären Blocker, der vorwiegend, wenn auch nicht ausschließlich, durch Blockade postsynaptischer Cholinrezeptoren wirkt. Es wurde bestätigt, daß eine der Haupteigenschaften von Org NC45 sein ungewöhnlich rascher Wirkungseintritt bei gleichzeitig hoher Aktivität ist. Die ausgesprochen deutliche Antagonisierung des Blocks, die einem kurzen Tetanus folgt, ließ vermuten, daß Org NC45 leichter von den cholinergen Endplattenrezeptoren verdrängt wird als Tubocurarin oder Pancuronium. Das führte, durch Versuche unterbauert, zu der Vorstellung, daß Edrophonium ein effektiverer Antagonist für Org NC45 ist als für die meisten anderen neuromuskulären Blocker. Edrophonium war ein etwa 12 mal schwächer wirsamer Antagonist von Org NC45 als Neostigmin. Die Wiederherstellung der Erregerübertragung auf den Kontrollwert (wie durch den "train-of-four"-Test gemessen) jedoch erfolgte durch Edrophonium mindestens doppelt so schnell wie mit Neostigmin und, vas noch wichtiger ist, Edrophonium bewirkte eine viel schwächere Wirkung des N. vagus auf das Herz als neostigmin. Die Ergebnisse, die an Katzen mit Edrophonium erzielt worden sind, wurden im wesentlichen durch Vorstudien an 9 narkotisierten Patienten bestätigt. In diesen Studien fand man, daß eine Dosis von 0,5 mg kg^{-1} i.v. rasch und ausreichend die Wirkung von Org NC45 antagonisiert. Wegen der relativ schwachen Nebenwirkungen brauchten 30 s vor Edrophonium-Gabe nur 0,6 mg Atropin (ca. 9 μg kg^{-1}) gegeben werden, was nur halb soviel ist wie man braucht, wenn man Neostigmin als Antagonist verwendet. Diese vorläufigen Beobachtungen an Patienten lassen vermuten, daß Edrophonium das Mittel der Wahl ist zur Antagonisierung von Org NC45.

ALGUNOS EFECTOS DEL ORG NC45 Y DEL EDROFONIO EN EL GATO Y EN EL HOMBRE ANESTESIADOS

SUMARIO

Se han estudiado algunos de los efectos de la droga relajadora de musculos, Org NC45, sobre el músculo anterior de la tibia de gatos sometidos a los efectos de la anestesia efectuada mediante cloralasas barbituradas. Sus efectos fueron los característicos de un agente de bloqueo neuromuscular que actúa bloqueando los colinoceptores de la unión posterior, predominantemente, aunque no de forma exclusiva. Se confirmó que una de las características importantes de la actividad del Org NC 45 es el que su efecto termina rápidamente a pesar de su gran potencia. La fuerte neutralización del bloqueo a raiz de la introducción de una inyección de tétano sugirió que el Org NC 45 se desplaza de los colinoceptores de la placa extrema más fácilmente que la tubocuranina o el pancuronio, lo que llevó a la hipótesis, confirmada por experimentos, de que el edrofonio sería un neutralizador del Org NC 45 más efectivo que la mayoría de las otras drogas de bloqueo neuromuscular. El edrofonio fue 12 veces menos potente que la neostigmina a la hora de neutralizar el Org NC 45. No obstante, y en base a dosis neutralizadoras equipotentes, el edrofonio volvió a colocar la transmisión bajo control (con arreglo a la prueba de cuatro impulsos efectuada) con una rapidez que por lo menos fue doble de la obtenida con la neostigmina y, lo que es más importante, el edrofonio ejerció un efecto mucho más débil sobre el vago cardiaco que la neostigmina. Los resultados obtenido de la aplicación de edrofonio en gatos se confirmaron en términos generales en los estudios preliminares efectuados en nueve pacientes anestesiados. En estos estudios se vió que una dosis intravenosa de 0,5 mg kg^{-1} de edrofonio produjo una neutralización del Org NC 45 rápida y adecuada y puesto que los efectos secundarios del edrofonio son relativamente débiles, fue necesario administrar, unos 30 minutos antes del edrofonio, 0,6 mg de atropina (unos 9 μg kg^{-1}) tan sólo, lo que equivale a la mitad de la dosis normalmente utilizada cuando el agente neutralizador es la neostigmina. Estas observaciones preliminares efectuadas en el hombre sugieren que el edrofonio puede ser el agente neutralizador necesario para el Org NC 45.

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HYDROGEN BONDING IN MECHANISMS OF ANAESTHESIA TESTED WITH CHLOROFORM AND DEUTERATED CHLOROFORM

S. WOOD, B. WARDLEY-SMITH, M. J. HALSEY AND C. J. GREEN

SUMMARY

There has been recent speculation about the role of hydrogen bonding in molecular mechanisms of anaesthesia. We have tested this hypothesis by comparing the potencies of chloroform and deuterated chloroform in mice, using loss of righting reflex as the endpoint for anaesthesia. We found that the ED_{50} for chloroform was 0.297 ± 0.03% (SD) and for deuterated chloroform 0.318 ± 0.02% (SD). These values are not significantly different. However, there were some differences in toxicity with deuterated chloroform having less "acute" toxicity. This is compatible with an isotope effect in which deuterium interferes with the formation of reactive free radicals. We conclude from the potency data that hydrogen bonding can be excluded as the major mechanism of chloroform anaesthesia.

It is now generally agreed that anaesthetics exert their effect by acting within a hydrophobic region of a cell, but the precise location of the anaesthetic molecule is still unknown, as is the type of molecular bonding involved. It has been suggested that van der Waals' forces are involved (Wulf and Featherstone, 1957), but there has been recent speculation on the role of hydrogen bonding (H-bonding) in the mechanism of narcosis of some agents. Halogenated anaesthetics are capable both of breaking existing H-bonds in macromolecules and subsequently forming H-bonds themselves. These bonds will be stronger in anaesthetics, such as halothane and chloroform, that contain acidic hydrogen (Sandorfy, 1980).

Almost all published studies of H-bonding of anaesthetics have involved *in vitro* model systems. For example, the ability of halogenated anaesthetics to affect H-bonds in model solvents such as N-ethylacetamine and tertiary butanol has been studied using infra-red spectroscopy (Trudeau et al., 1978). Nuclear magnetic resonance has also been used to study halothane in artificial membranes (Koehler, Curley and Koehler, 1977). Few data are available concerning the role of hydrogen-bonding in *in vivo* anaesthesia. One method of testing if it plays a major part in the mechanism of action of the anaesthetic is to substitute deuterium for hydrogen in the anaesthetic molecule. Deuterium forms slightly stronger H-bonds than hydrogen, as illustrated by the fact that the boiling point of "heavy water" (D_2O) (101.4 °C) is greater than that of water (H_2O) (100 °C).

In this study, we compared the potency of chloroform ($CHCl_3$) with deuterated chloroform ($CDCl_3$) in mice, using loss of righting reflex as the endpoint for anaesthesia. If H-bonding were an important factor in the molecular mechanism of action of these agents, then their potencies should differ. In addition, we compared the relative toxicities of these agents, as it has been suggested that deuteration reduces the toxicity of halogenated anaesthetics (McCarty, Malek and Larsen, 1979).

MATERIALS AND METHODS

Potency

Male T-O strain mice (25–35 g) were used in all experiments. Groups of eight mice were exposed to either chloroform ($CHCl_3$) or deuterated chloroform ($CDCl_3$) in a 20-litre glass and metal chamber designed to minimize uptake of anaesthetic into the apparatus. The mice were placed in individual cages which could be rotated; in addition two mice with rectal probes were placed in non-rotating cages. Chamber temperature was controlled to maintain the rectal temperature of the mice at 37 ± 1 °C.

Loss of righting reflex was taken as the means of determining anaesthetic potency (Miller et al., 1972). The cage was rotated at 5 rev min^{-1} every 5 min; the endpoint was taken when a mouse failed to right itself for two revolutions.

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The concentration of anaesthetic was increased by the addition of liquid $CHCl_3$ or $CDCl_3$. A known amount of anaesthetic was slowly injected from a glass syringe through a metal needle in the door of the chamber and evaporated by a fan inside the chamber. The inspired concentration was determined by calculation based on the volume of liquid added:

$$\% \, CHCl_3 = \frac{X \times \text{sp.gr}}{\text{mol. wt.}} \times \frac{22.414}{V} \times \frac{101}{p_B} \times \frac{T}{273} \times 100\%$$

where X = volume of liquid $CHCl_3$ (ml)
sp. gr. = specific gravity (1.47)
mol. wt. = molecular weight (119.4)
V = volume of chamber (litre)
p_B = barometric pressure (kPa)
T = room temperature (K)

In addition, it was measured by gas chromatography (flame ionization detector) with samples taken from a sampling line in the same area as the rotating cages. Each concentration was kept constant for a minimum of 20 min before the endpoint was accepted, which was found to be sufficient to establish equilibrium. The concentration was increased or decreased in a series of small stages until all eight mice had lost their righting reflex. It was then reduced to approximately 0.5 ED_{50} and the number of mice recovering their righting reflex noted.

Soda-lime was not used, to avoid any possibility of formation of toxic breakdown products. However, carbon dioxide concentrations were measured using an infra-red analyser and were found to be less than 0.1% throughout the experimental period which never exceeded 3 h.

Before commencing potency determinations of $CHCl_3$ and $CDCl_3$, the apparatus was used to determine the potency of halothane which was compared with previously published results as a check on the validity of the method.

Toxicity

Preliminary experiments indicated that there might be a difference between the toxicity of $CHCl_3$ and $CDCl_3$. This was assessed using 10 mice for each agent. At the end of exposure, the number recovering their righting reflex at approximately half the ED_{50} was noted. Five animals were then sacrificed immediately after anaesthesia and specimens of heart, spleen, lung, liver and kidney removed and preserved in formol saline for subsequent histology. The remaining five animals in each group were sacrificed 6 h ($CHCl_3$) or 24 h ($CDCl_3$) after exposure, with the same organs being preserved for histology.

RESULTS

Potency

Results for the potency determinations of halothane are shown in figure 1. The ED_{50} was found to be 0.72±0.11% (SD) ($r = 0.84$), which compared favourably with other published values, such as 0.77% (Kent et al., 1977) in mice (Swiss Webster strain) and 0.90% (White, Johnston and Eger, 1974) in Sprague–Dawley rats.

Results for the potencies of chloroform and deuterated chloroform are shown in figure 2. The data were plotted as probit response *v.* log dose and ED_{50} calculated using linear regression. ED_{50} for chloroform was 0.297±0.03% (SD) ($r = 0.81$) and for deuterated chloroform, 0.318±0.02% (SD) ($r = 0.71$). These values are not significantly different.

Toxicity

Results of the toxicity study are presented under the headings of recovery of righting reflex after anaesthesia and histopathology. There was a marked difference in "acute toxicity" between the

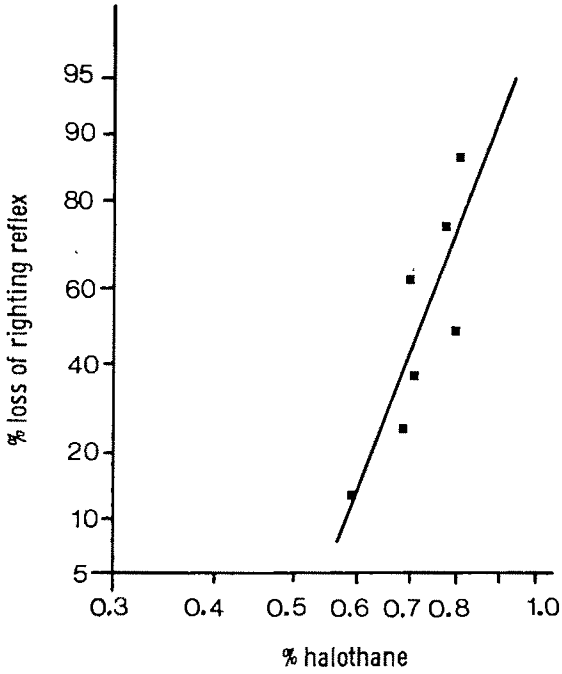

FIG. 1. Dose–response data for halothane on a log-probit plot.

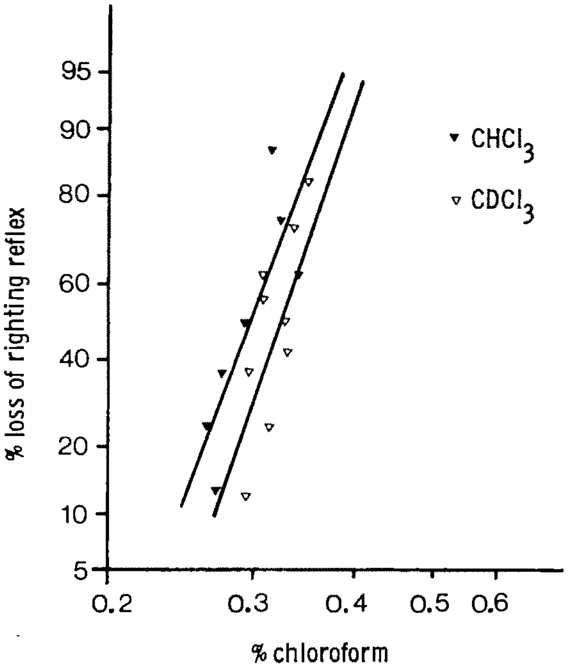

FIG. 2. Dose–response data for chloroform (▼) and deuterated chloroform (▽) on a log-probit plot.

two agents. Only four of the 47 mice (8.5%) regained their righting reflex on reducing the concentration of chloroform to half the ED_{50}. The remaining mice showed no sign of returning righting reflex after periods up to 1 h at this concentration. In contrast, after reducing the concentration of deuterated chloroform to half the ED_{50}, 28 of 55 (51%) regained their righting reflex. Equivalent studies with halothane showed a 100% recovery of righting reflex after 20 min at a concentration of half the ED_{50}.

Results of histological analyses are shown in table I. No abnormality was seen immediately after $CHCl_3$ anaesthesia although two animals died during the anaesthetic. Some early changes in liver and kidney were seen in the group sacrificed at a maximum of 6 h after anaesthesia. In this group, three mice died between 3 and 6 h after anaesthesia and at 6 h the remaining two animals were comatose.

The group exposed to deuterated chloroform showed early kidney tubular necrosis immediately after anaesthesia even though short-term recovery was better in this group. All animals in the second $CDCl_3$ group survived for 24 h after anaesthesia although they were comatose at this time. Histological changes were more pronounced, including liver and kidney changes and some evidence of inflammatory oedema.

TABLE I. *Toxicity results (histology). *Two of five died during anaesthesia; †three of five died 3–6 h after anaesthesia; ‡two of five sacrificed 6 h after anaesthesia. — = no abnormality found*

	Heart	Liver	Kidney	Spleen	Lung
$CHCl_3$					
Group I*	—	—	—	—	—
Group II†‡	—	Mild cent. lobular necrosis	V. mild tubular necrosis	—	—
$CDCl_3$					
Group I	—	—	Mild tubular necrosis	—	—
Group II (24 h)	—	Central lobular necrosis	Tubular necrosis	—	2/5 Inflamm.

DISCUSSION

Predictions concerning the expected difference in potency between deuterated and non-deuterated anaesthetics are based solely on studies in model systems and these studies are also subject to varying interpretations. For example, differences in the relative strengths of intermolecular hydrogen bonding are demonstrated by the different boiling points of $CHCl_3$ and $CDCl_3$. However, these are no indication of the predicted differences in anaesthetic potencies because they reflect differences in the association of the molecules with themselves and not with a potential site of action. There are also problems with interpreting model solvent studies. The temperature shifts in the infra-red spectra of $CDCl_3$ have been measured in various solvents (Sandorfy, 1980) and it has been predicted that the shift in the C–D stretching band would be twice as large for $CHCl_3$. Since we do not know the exact role of hydrogen bonding or the correct model solvent for the unknown site, it is impossible to predict *in vivo* potencies. However, if H-bonding played a major role in anaesthesia the difference in $CHCl_3$ and $CDCl_3$ potency should be significant.

It might be argued that our method of assessing anaesthetic potency was not sufficiently sensitive, but the average coefficient of variation for the three ED_{50} was 9%. This is as good, if not better, than any other potency studies of which we are aware. The use of the loss of righting reflex in mice is already established as a reproducible method of assessing anaesthetic potency and, although there are possible exceptions, the data correlate with those for surgical anaesthesia in man (Kent et al., 1977). The present experiments indicate that any differences, if they exist at all, must be very small and do not appear to justify extension of the work to other species or other endpoints.

In contrast to the similarities in potency, there are major differences in toxicity between $CHCl_3$ and $CDCl_3$. The morbidity and mortality of the mice following chloroform anaesthesia was high (table I). Deuterated chloroform had less immediate toxicity and the mice survived longer. It would appear that the subsequent histological changes in the liver and kidney were more pronounced with $CDCl_3$, but this probably reflects the fact that they survived up to the intended sacrifice time (24 h) whereas those exposed to $CHCl_3$ did not. For these and other reasons (Green, 1979), chloroform is unequivocally contraindicated for rodent anaesthesia.

These toxicity data agree both with the theoretical considerations of chloroform biotransformation and with previous data on deuteration of anaesthetics. The toxicity of chloroform in man is thought to be caused by formation of highly reactive free radicals such as $\cdot CCl_3$ and $:CCl_3$ (Van Dyke, 1969). Their formation is related to the reactivity of the C–H and C–D covalent bond. Deuteration to $CDCl_3$ slows this process but does not prevent it completely. This is supported by the toxicity data obtained 24 h after anaesthesia. This study did not measure enzyme concentrations but McCarty, Malek and Larsen (1979) analysed serum glutamic pyruvic transaminase following exposure of rats to $CHCl_3$ and $CDCl_3$. They did not present their data in terms of the percentage of animals with concentrations greater than normal, but it was clear that the concentrations for animals exposed to $CDCl_3$ were less than those exposed to $CHCl_3$.

We conclude from the anaesthetic potency data that the lack of significant differences between $CHCl_3$ and $CDCl_3$ excludes hydrogen bonding as a major factor in their molecular mechanisms. The study does not exclude the partial or weak involvement of this type of association for these or other agents, but the general thesis of the role of hydrogen bonds in anaesthesia appears to be less likely than has previously been argued. However, major differences in toxicity suggest that the reactivity of the covalent bond is a factor affecting toxicity related to biotransformation.

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LA LIAISON HYDROGENE DANS LES MECANISMES DE L'ANESTHESIE TESTES AVEC DU CHLOROFORME ET DU CHLOROFORME MARQUE AU DEUTERIUM

RESUME

Un certain nombre d'hypothèses ont été avancées récemment sur le rôle de la liaison hydrogène dans les mécanismes moléculaires de l'anesthésie. Nous avons mis ces hypothèses à l'épreuve en comparant les puissances du chloroforme et du chloroforme marqué au deutérium chez des souris en utilisant la perte du réflexe de redressement comme critère d'anesthésie. Nous avons constaté que la DE_{50} du chloroforme était 0,297 ± 0,03% (DS) et celle du chloroforme marqué au deuterium de 0,318 ± 0,02% (DS). Ces valeurs ne sont pas significativement différentes. Il existe cependant quelques différences de toxicité, le chloroforme marqué au deuterium ayant une toxicité 'aiguë' moindre. Ceci est compatible avec un effet de l'isotope dans lequel le deuterium interfèrerait dans la formation de radicaux libres réactifs. Les données sur la puissance des deux anesthésiques nous permettent de conclure que la liaison hydrogène peut être rejetée comme mécanisme principal de l'anesthésie par le chloroforme.

UNTERSUCHUNG DER HYDROGENBINDUNG ALS WIRKMECHANISMUS DER NARKOSE BEI VERWENDUNG VON NORMALEM CHLOROFORM UND DEUTERIUMCHLOROFORM

ZUSAMMENFASSUNG

In der letzten Zeit vermutete man, daß die Hydrogenbindung eine Rolle bei den molekularen Mechanismen der Narkose spielt. Wir prüften diese Hypothese durch Vergleich der Potenz von Chloroform mit Deuteriumchloroform an Mäusen und nahmen als Beginn der Narkose den Verlust des Stellreflexes. Wir fanden daß die ED_{50} von Chloroform bei 0,297 ± 0,03% (SD) und für Deuteriumchloroform bei 0,318 ± 0,02% (SD) lag. Diese Werte sind nicht signifikant verschieden, jedoch war die "akute" Toxizität von Deuteriumchloroform geringer. Dies ist mit einem

Isotopeneffekt vereinbar, bei dem Deuterium die Bildung von reaktionsfähigen freinen Radiakalen beeinträchtigt. Anhand der Werte über die Wirkstärke kann die Hydrogenbindung als Hauptmechanismus der Chloroformnarkose ausgeschlossen werden.

ENLACES DEL HIDROGENO EN LOS MECANISMOS DE ANESTESIA COMPROBADOS CON CLOROFORMO Y CON CLOROFORMO DEUTERADO

SUMARIO

Recientemente ha habido una cierta especulación sobre el papel que juegan los enlaces del hidrógeno en los mecanismos moleculares de la anestesia. Hemos puesto a prueba esta hipótesis al comparar en ratones las potencias del cloroformo y del cloroformo duterado, usando la pérdida del reflejo de enderezamiento como el punto final de la anestesia. Averiguamos que para el cloroformo el ED_{50} fue de 0,297 ± 0,03% (error cuadrático medio) y que para el cloroformo deuterado fue de 0,318 ± 0,02% (error cuadrático medio). Estos valores no son significativamente diferentes. Sin embargo hubo algunas diferencias de toxicidad y el cloroformo deuterado presentó una toxicidad menos "aguda". Esto es compatible con el efecto isotópico en el que el deuterio interfiere en la formación de radicales reactivos libres. Concluimos a raiz de los datos sobre la potencia que el enlace del hidrógeno puede excluirse como el mecanismo principal de la anestesia por cloroformo.

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PLASMA CONCENTRATION AND E.E.G. AFTER VARIOUS REGIMENS OF ETOMIDATE

A. DOENICKE, B. LÖFFLER, J. KUGLER, H. SUTTMANN AND B. GROTE

SUMMARY

Etomidate was injected i.v. within 10 or 60 s at various doses. After etomidate 0.3 mg kg^{-1} the plasma concentration was 1.6 $\mu g\ ml^{-1}$ at 1 min after the end of injection. For about 7 min a good hypnotic effect (stages C_0–D_2) was observed on the e.e.g. recording. For surgical procedures, however, a combination with analgesic drugs appeared to be necessary. When the dose of etomidate was increased (0.1–0.4 mg kg^{-1}) a linear increase in plasma concentration and slow e.e.g. activity was observed concomitantly. Anaesthesia could be prolonged with additional injections or with continuous infusion. Each additional injection produced a steep increase in concentration of short duration with marked deepening of hypnosis. The infusion induced only a moderate increase in plasma concentration, whereas the depth of sleep during the period of infusion remained nearly the same. E.e.g. changes induced by etomidate are similar to those after barbiturates and other i.v. anaesthetics.

Following the initial animal experiments carried out at Janssen Pharmaceutica (Janssen et al., 1971), etomidate was first used by two of the authors in 1972 in man under e.c.g. and e.e.g. control. After further experimental studies and 8 years of clinical research, this substance became a successful short-acting hypnotic with minimal effects on the circulation (Brückner et al., 1974; Doenicke et al., 1974; Kettler et al., 1974). The possibility of histamine release can almost be excluded (Doenicke, Lorenz et al., 1973).

That hypnosis could be prolonged by additional injections of etomidate has been known for some time and has been confirmed by e.e.g. recordings (Doenicke, Kugler et al., 1973). However, for such clinical applications there was a lack of information on the plasma concentration.

At the end of 1974 Wynants, Woestenborghs and Heykants published a method enabling investigators to determine etomidate in the plasma by gas chromatography, using the unlabelled drug. By means of this procedure, we have established the plasma concentration occurring after different etomidate regimens and compared these results with the e.e.g. findings (Doenicke et al., 1975).

SUBJECTS AND MATERIALS

Fifteen healthy male volunteers, aged 20–30 yr, took part in this study, giving informed consent.

Group 1

Six subjects received etomidate 0.3 mg kg^{-1} at 2-week intervals, on the first occasion over 10 s and on the second occasion over 60 s.

Group 2

Six subjects each received etomidate 0.3 mg kg^{-1} over 60 s followed by 0.15 mg kg^{-1} over 60 s at 5 min and at 12 min. Two weeks later they received the same initial dose (0.3 mg kg^{-1}) followed by 0.3 mg kg^{-1} in 250 ml of glucose as a continuous infusion injected between the 5th and 14th min.

Group 3

Three subjects each received, at 10-day intervals, a total of four anaesthetics. Etomidate was injected in increasing doses, 0.1, 0.2, 0.3 and 0.4 mg kg^{-1}, always within 10 s.

Premedication was the same for all groups: atropine 0.5 mg 15 min before the start of anaesthesia, diazepam 0.05 mg kg^{-1} 10 min before, and fentanyl 0.1 mg i.v. 5 min before. Diazepam and fentanyl were given to avoid the occurrence of myoclonic movements.

Blood 8 ml was sampled from an arm vein at the

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following times: for the anaesthetics with a single injection, 1, 2, 4, 8, 16 and 32 min after the end of injection; for the anaesthetics with additional injections and continuous infusion 1, 2, 4, 7, 9, 14, 16, 20, 28, 44, and 60 min after the end of injection. The blood was stored in cooled test tubes containing sodium citrate and potassium fluoride. Blood samples were centrifuged at 3000 rev min^{-1} and plasma was separated from the blood.

For gas chromatographic determination propoxate 1 μg (propyl-phenyl-ethyl-1H imidazol-5-carboxylate) was added to the plasma and used as internal standard. This standard was used throughout the chemical extraction of the substance.

The gas chromatograph was a Varian 2140 with an alkali flame ionization detector. After the injection of the sample to the gas chromatograph the peak of etomidate appeared first, followed by that of propoxate. The amount of etomidate in the sample was measured by a comparison of these two peaks. Concentrations of etomidate between 0.01 $\mu\text{g ml}^{-1}$ and 10 $\mu\text{g ml}^{-1}$ could be measured. The error was 5% for the greater concentration (10 $\mu\text{g ml}^{-1}$) and 20% for the lesser concentration (0.01 $\mu\text{g ml}^{-1}$) (Wynants, Woestenborghs and Heykants, 1974).

TABLE I. *Classification of depths of sleep (vigilosomnogram). L = Loomis; K = Kugler*

	L	K	
Mental relaxation	A	A_0	Distribution of α-rhythm as seen in normal e.e.g.-tracing.
Very slight sleep		A_1	Diffusion of α-rhythm. Dimunition of α-frequency (in some e.e.g. after preceding increase of the amplitude).
		A_2	α-waves become smaller and scarcer, an "off-effect" still existing.
	B	B_0	Low θ-waves. Sensory stimuli may remain ineffective.
		B_1	Diffuse θ-waves of increasing amplitude, small and fast activity in the central regions.
		B_2	Appearance of small vertex-waves; after arousal stimuli, reactivation of α-waves (return to stage A).
Light sleep	C	C_0	Diffuse θ-activity, random δ-waves. Spindles of fast waves in the precentral regions (σ-rhythms) and K-complex after sensory stimuli.
		C_1	σ-rhythms of increasing amplitude ("sleep spindles") and K-complexes.
		C_2	Temporal transition to δ-waves, stretched K-complexes; after arousal stimuli return to B or A.
Moderately deep sleep	D	D_0	δ-sines up to 30% of time, slowing σ-rhythms, irregular K-complexes.
		D_1	High δ-waves during 50% of time.
		D_2	Predominating slow δ-waves during 80% of time. After intensive arousal stimuli return to stage C.
Very deep sleep	E	E	Continuous high δ-activity, no isolated K-complexes or σ-rhythms; after arousal stimuli, synchronous, slow waves or lack of reactions.

From the time of premedication, the e.c.g. and arterial pressure (Riva-Rocci) were monitored continuously. The e.e.g. was recorded on a 12-channel Hellige-apparatus (Kugler, Doenicke and Laub, 1977).

The e.e.g. curves were evaluated visually and classified according to the e.e.g. stages in each successive 40-s epoch (table I) and then illustrated in a compressed time-scale giving a display of the spectrum of vigilance and sleep (vigilosomnogram).

The following time points of the spectrum were compared with the corresponding plasma concentrations:

(a) period of latency: the period between the start of the injection and the first e.e.g. changes.

(b) end of peak activity: the time when the vigilosomnogram changed from C_0 to B_2.

(c) end of activity: return to superficial stages of sleep or to awakening (A_1, A_2, B_0).

RESULTS

The e.e.g. stages after the administration of etomidate were comparable to the e.e.g. patterns after barbiturates and other i.v. anaesthetics. After a period of latency lasting 10–30 s (depending on the speed of injection), a short initial activation phase of a few seconds occurred with 6–10 s e.e.g. activity (fig. 1).

Subsequently, this e.e.g. changed very rapidly to high, slower activity with superimposed lower, rapid waves. When hypnotic activity subsided, mixed activity decreased and more prolonged, slow waves were observed over the posterior region of the brain. Paroxysmal, or burst suppression, activities did not occur.

Rapid and slow injection (fig. 2)

Group 1. Within the first minute after the end of injection, peak plasma concentrations of 1.59 (0.48–2.67) $\mu\text{g ml}^{-1}$ were reached after rapid injection; 1.30 ± 0.38 $\mu\text{g ml}^{-1}$ after slow injection. All the data presented here were expressed as mean values

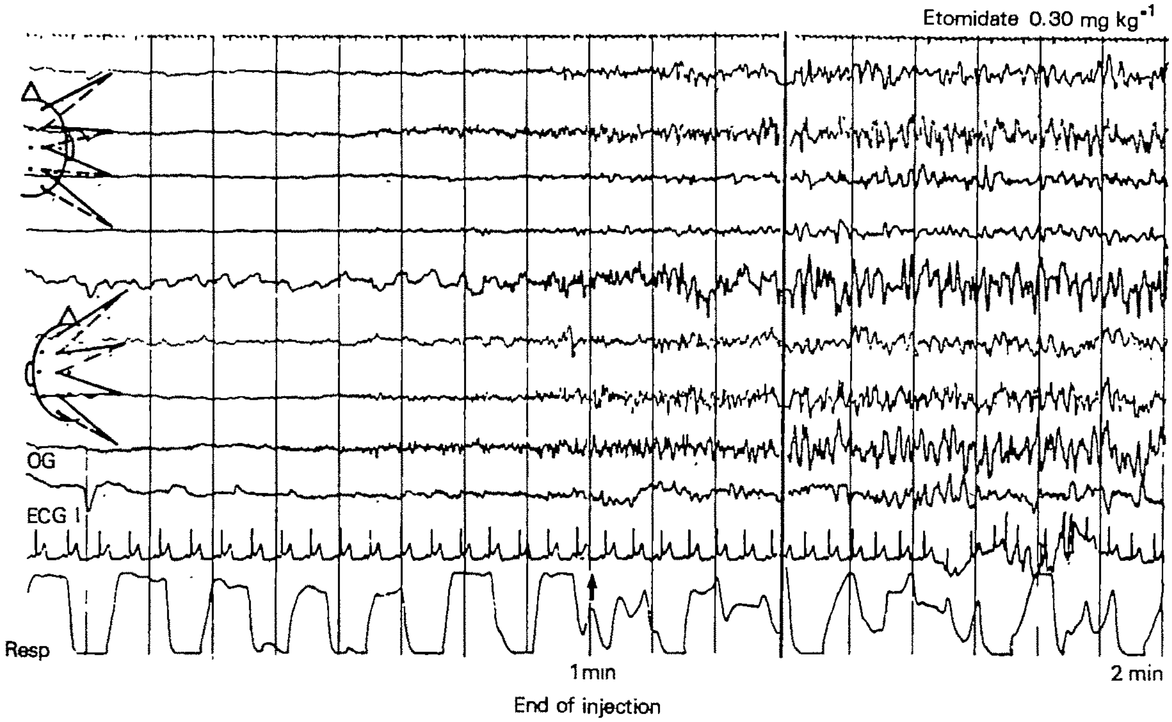

FIG. 1. Etomidate-induced e.e.g.-changes (healthy volunteer): 10 s before the end of injection (0.3 mg kg^{-1} within 1 min) relatively fast irregular activity. At the end of the injection (1 min, ↑) small slow waves. One minute later (2 min) high slow activity, superimposed fast waves. The oculogram (OG; right to left epicanthus) shows decreasing rapid eye movements of wakefulness. In the e.c.g. (ECG I) increasing heart rate (up to 88 beat min^{-1}). Respiration irregular, relatively fast (22 b.p.m.).

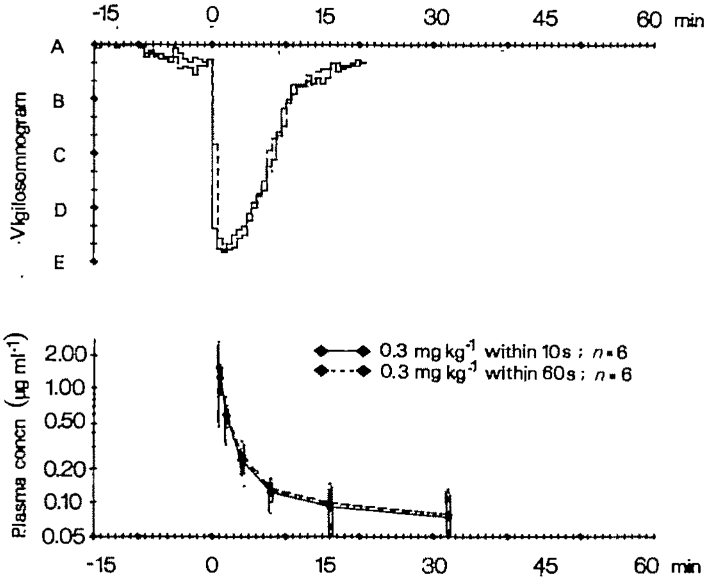

FIG. 2. Vigilosomnogram after a bolus injection of etomidate 0.3 mg kg^{-1} and corresponding etomidate concentrations in the plasma. Premedication: −15 min, atropine 0.5 mg; −10 min, diazepam 0.05 mg kg^{-1}; −5 min, fentanyl 0.1 mg.

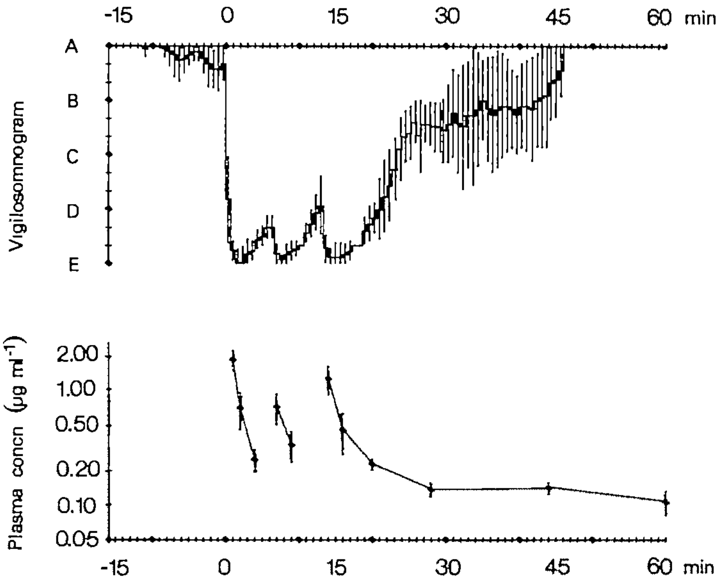

FIG. 3. Vigilosomnogram (mean values ± SD) of prolonged anaesthesia. Additional injections of etomidate 0.3 mg kg^{-1} (60 s at 0 min), 0.15 mg kg^{-1} (60 s at 5 min), 0.15 mg kg^{-1} (60 s at 12 min), and corresponding etomidate concentrations in the plasma. Premedication −15 min, atropine 0.5 mg; −10 min, diazepam, 0.05 mg kg^{-1}; −5 min, fentanyl 0.1 mg.

± SD. At 1 min plasma concentration was approximately 0.6 µg ml^{-1}, and at 32 min the concentration was approximately 0.075 µg ml^{-1} with both types of injection.

The end of peak activity occurred after 427 ± 85 s for the rapid injection and after 440 ± 112 s for the slow injection, both read from the e.e.g. (fig. 2). The difference was not statistically significant. The total duration of sleep did not differ substantially either: 770 ± 218 s after the rapid injection *v.* 700 ± 185 s after the slow injection. The plasma–time diagrams revealed an etomidate concentration of 0.14 µg ml^{-1} at the end of peak activity and of 0.11 µg ml^{-1} at the end of activity.

Prolongation of anaesthesia by additional injections or continuous infusion (fig. 3)

Group 2. Up to the 4th min the same pronounced initial decrease in concentration observed in the first group was noticed. Thereafter, each additional injection, as expected, produced a pronounced, rapid increase in plasma concentration; the subsequent decrease in concentration resembled that of the first injection.

Each additional injection had an effect on the depth of sleep as noted in the e.e.g. (fig. 3, upper part). After 22 min individual values showed considerable variation with a tendency to deep, posthypnotic stages.

No such changes in plasma concentration were noted when etomidate was administered by continuous infusion (fig. 4). From 0.34 ± 0.06 µg ml^{-1} at the beginning of the infusion, the plasma concentration increased to 0.54 ± 0.12 µg ml^{-1} at the end of the infusion; at 20 min no difference was apparent between bolus injection and infusion. The peak of activity after both regimens lasted about 22 min, whereas the end of activity appeared at about 34 min.

Increasing dose of etomidate

Group 3. The vigilosomnogram (fig. 5A) showed that increasing doses of etomidate produce a deeper and longer hypnotic effect. There was a good relationship between plasma concentration and the observed changes in vigilosomnogram (fig. 5B). The plasma concentration of etomidate at the end of peak activity was 0.12 ± 0.04 µg ml^{-1} at a dose of 0.1 mg kg^{-1} and 0.22 ± 0.05 µg ml^{-1} at 0.4 mg kg^{-1} ($P < 0.05$). By increasing the doses of etomidate "acute tolerance" was observed (fig. 6) as it has been described for barbiturates (Brodie et al., 1951; Dundee, Price and Dripps, 1956; Maynert and Klingmann, 1960).

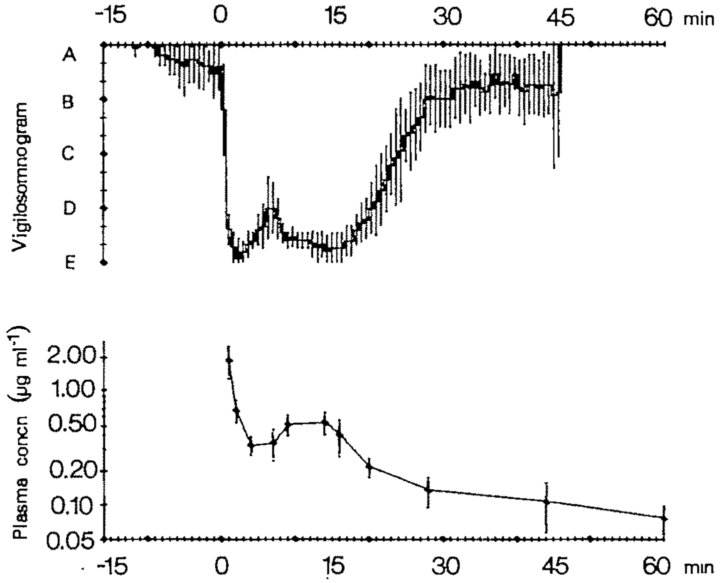

FIG. 4. Vigilosomnogram (mean values ± SD) with continuous infusion of etomidate 0.3 mg kg^{-1} in glucose 250 ml from 5 min to 14 min (0.3 mg kg^{-1} given over 60 s at 0 min). Premedication: −15 min, atropine 0.5 mg; −10 min, diazepam 0.05 mg kg^{-1}; −5 min, fentanyl 0.1 mg.

Kinetics of etomidate

The clear biphasic decrease in the plasma concentration curve after a single bolus injection can be explained by means of a two-compartment open model.

After a rapid injection, etomidate immediately entered the central or distribution compartment, represented by the intravascular volume, which is the sole compartment involved in excretion. There is a rapid exchange between this compartment and the effector compartment c.s.f. and specific receptors, where the drug exhibits its activity (Dost, 1968). Both distribution spaces can be regarded as a common reference compartment with a volume of 7.5 litre.

In addition to the plasma, this compartment also comprises well-perfused organs. The half-life of etomidate of 1 min for this compartment correlates well with the short hypnotic activity of the drug.

After 8 min the concentration decreased less rapidly than before, maintaining an equilibrium between plasma and tissue concentrations (zero exchange of drug). The changes in this phase correspond with the elimination of drug.

The distribution volume for etomidate was 145 litre, the elimination constant 0.03 min and the elimination half-life 29 min.

DISCUSSION

At pH 7.4 etomidate was 65% bound to albumin, the total binding to human plasma being substantially greater (90%). Etomidate is thus one of the substances with very high protein binding (Mannes and Doenicke, 1977). This might explain why the differences between the effects of rapid and slow injections are so small with regard to plasma concentration and hypnotic activity. A conspicuous feature in this respect is the fluctuation of measured values during the 1st min following a single rapid injection. In some subjects, the processes of distribution probably occur at such a rapid rate that at the time of measuring a large proportion of the drug has already been carried to well perfused organs.

In recent studies, the detection limit for unlabelled etomidate could be lowered still further by perfecting the method devised by Wynants (van Hamme, Ghoneim and Ambre, 1978; Schüttler, Wilms et al., 1980). Thus, Schüttler, Wilms and others (1980) succeeded in following the pathways of etomidate up to 4 h after a bolus injection; van Hamme, Ghoneim and Ambre (1978) extended this to 10 h.

Kinetic data obtained from their studies were different from those obtained by us (Schüttler: $T_{\frac{1}{2}} = 68$ min, $V = 161$ litre; van Hamme:

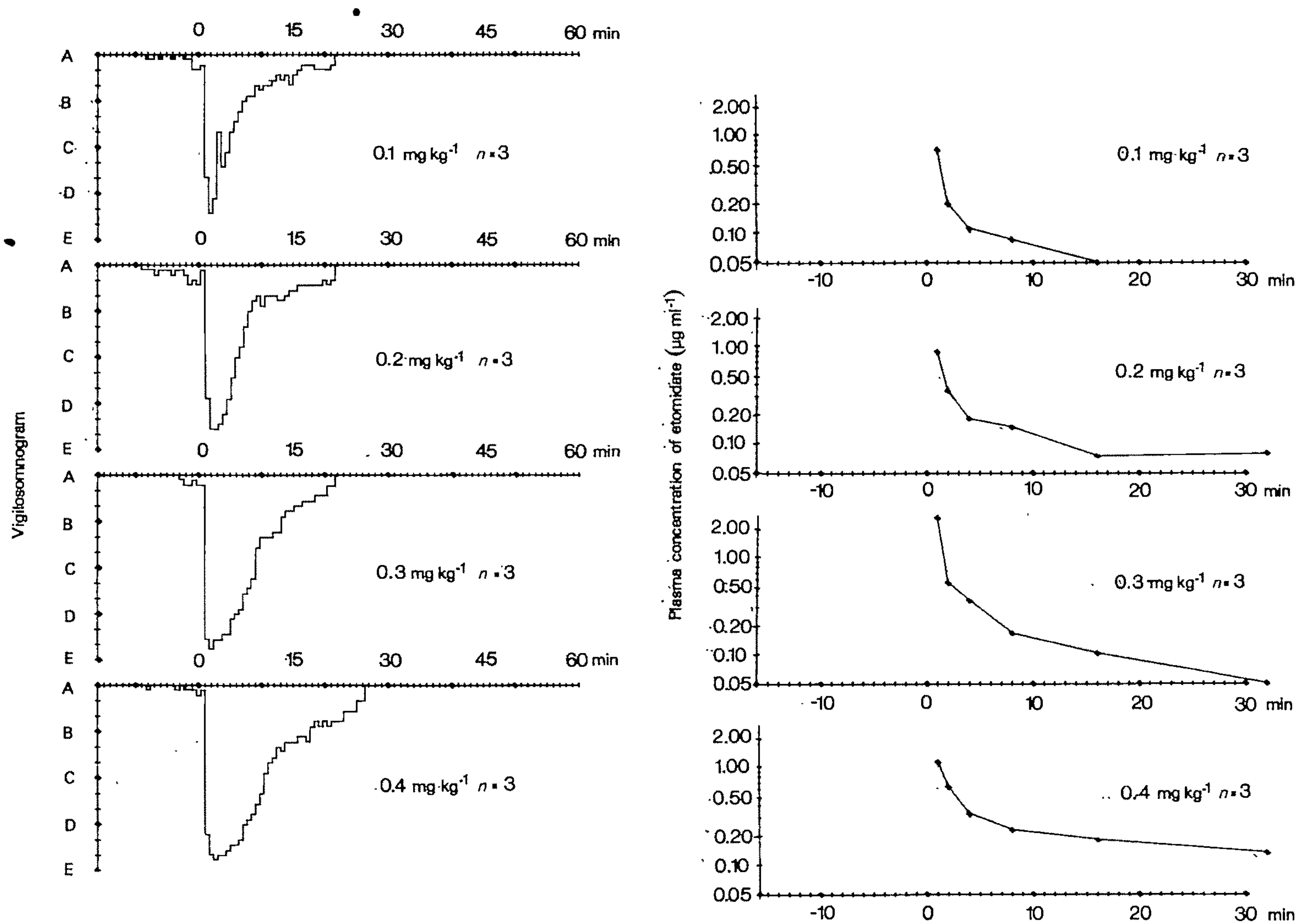

FIG. 5. Vigilosomnogram of increasing doses (left-hand part of figure) corresponding with etomidate concentrations in the plasma (right-hand graphs). Premedication: −15 min, atropine 0.5 mg; −10 min, diazepam 0.05 mg kg^{-1}; −5 min, fentanyl 0.1 mg.

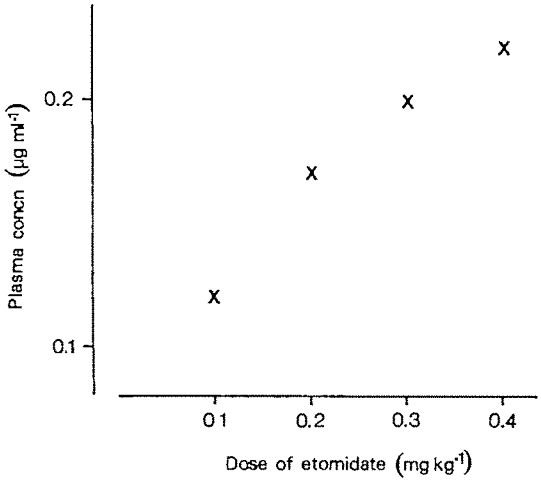

FIG. 6. Acute tolerance under etomidate. Etomidate concentration at the end of peak activity at increasing doses.

$T\frac{1}{2}=29$ min, $V=158$ litre (second compartment); our studies: $T\frac{1}{2}=29$ min, $V=145$ litre).

Both investigators, however, recorded their measurements in patients who underwent ophthalmic surgery lasting up to 3–5 h. Thus, the presence of other anaesthetic drugs might influence the plasma concentration of etomidate through biological changes.

Measurements by van Hamme started only after 4 min, and by Schüttler after 2 min, so that initial concentration peaks were not recorded and the plasma curve was too flat (van Hamme, Ghoneim and Ambre, 1978). This might explain why a three-compartment open model, used in their studies, showed the volume and etomidate half-life value for the central compartment to be great. Van Hamme (continuous measurements of the plasma concentration for 10 h) calculated by a three-compartment model a distribution volume of 335 litre and a half life of 4.6 ± 2.6 h. These data suggest that the last time-point in our measurements might not resemble an equilibrium state of the substance between plasma and tissue.

Because of the short half-life of etomidate, additional injections to prolong hypnosis have to be administered repeatedly. These are accompanied by high plasma concentrations which are reflected in pronounced e.e.g. depression.

In all volunteers, the depth of sleep decreased between 11 and 14 min, in two of them to the point at which the level was less than stage C_0. This suggests that the second additional injection should be given in the 10th min.

At the dose we chose for continuous infusion (0.3 mg kg^{-1}) corresponding to 2.4 mg min^{-1} the plasma concentration 5 min after the first injection increased from 0.34 µg ml^{-1} to 0.54 µg ml^{-1} and remained at that value until the end of the infusion. If the concentration becomes less than 0.19 µg ml^{-1} lighter sleep stages occur with wakening at values less than 0.12 µg ml^{-1} (fig. 4).

Schüttler, Stoeckel and others (1980) reported an infusion regimen with two different doses. Etomidate 80 mg was infused within 10 min to induce sleep. Subsequently, a plasma concentration of 0.5 µg ml^{-1} was maintained with etomidate 0.8 mg min^{-1}. Plasma concentration on recovery from sleep was approximately 0.3 µg ml^{-1}, 2.5 times greater than in our studies. The apparent reason for these discrepancies must be the absence of premedication in Schüttler's study. As a consequence, they noticed myoclonia in each volunteer at induction and recovery. It is worthwhile mentioning that the use of an analgesic (fentanyl, nitrous oxide) in clinical practice is very important when etomidate is used as an hypnotic drug.

The bolus injection of etomidate seems to us a safer form of induction than is the infusion, especially since etomidate 80 mg within 10 min represents a very high dose. Subsequently, the continuous infusion is set according to the patient's requirements, the premedication used and the type of surgery.

The dose we chose is certainly too great for prolonged anaesthesia. After 20 min a dose of 0.5–0.8 mg min^{-1} appeared to suffice. In a late study Schwilden and co-workers (1981) have shown that, after 30 min, this dose can be further decreased.

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CONCENTRATIONS PLASMATIQUES ET E.E.G. APRES DIFFERENTS PROTOCOLES D'ADMINISTRATION DE L'ETOMIDATE

RESUME

De l'etomidate a été injecté en 10 ou 60 s par voie intraveneuse à différentes posologies. Après 0,3 mg kg^{-1} d'étomidate, la concentration plasmatique était 1,6 μg ml^{-1} 1 min après la fin de l'injection. On a observé un bon effet hypnotique (états C_0–D_2) sur les enregistrements e.e.g. pendant environ 7 min. Il semble cependant nécessaire d'associer des analgésiques pour des actes chirurgicaux. Lorsque l'on a augmenté les posologies d'étomidate (0,1–0,4 mg kg^{-1}), on a observé simultanément une augmentation linéaire de la concentration plasmatique et de la durée d'action. L'anesthésie pouvait être prolongée par des injections supplémentaires ou une perfusion continue. Chaque injection supplémentaire entraînait une augmentation de concentration de courte durée et un approfondissement marqué de la narcose. La perfusion continue n'entrainait qu'une augmentation modérée de la concentration plasmatique, alors que la profondeur de la narcose restait pratiquement constante pendant la période de perfusion. Les modifications e.e.g. induites par l'étomidate sont les mêmes que celles observées aprés injection de barbituriques ou autres anesthésiques intraveineux.

ZUSAMMENFASSUNG

Etomidate wurde in verschiedenen Dosierungen intravenös innerhalb von 10 bzw. 60 s injiziert. Nach Etomidate 0,3 mg kg^{-1} Etomidate betrug die Plasmakonzentration 1 min nach Injektionsende 1,6 μg ml^{-1}, die Schlafphase (Stadien C_0–D_2) hielt nach den EEG-Aufzeichnungen 7 min an. Für chirurgische Eingriffe jedoch ist eine Kombination mit Analgetika erforderlich. Bei steigender Dosierung von Etomidate (0,1–0,4 mg kg^{-1}) ergaben sich linear steigende Plasmakonzentrationen und Wirkzeiten. Eine Narkoseverlängerung konnte mit Nachinjektionen als auch mit Tropfinsfusionen erzielt werden. Jede Nachinjektion bewirkte einen kurzzeitigen, steilen Konzentrationsanstieg mit deutlicher Narkosevertiefung. Durch die Tropfinsfusion stieg die Plamakonzentration nur mäßig an, die Narkosetiefe blieb während der Infusionszeit fast konstant. Etomidate bewirkte ähnliche EEG-Veränderungen wie Barbiturate und andere intravenöse Anästhetika.

CONCENTRACION DE PLASMA Y E.E.G. DESPUES DE VARIOS REGIMENES DE ETOMIDATA

SUMARIO

Se inyectaron por vía intravenosa varias dosis de etomidata a intervalos de 10 ó de 60 segundos. Al cabo de un minuto de haber administrado una inyección de 0,3 mg kg^{-1} de etomidata la concentración de plasma fue de 1,6 μg ml^{-1}. Por espacio de 7 minutos se observó un buen efecto hipnótico (fases C_0–D_2) en el registro del e.e.g. No obstante, para fines de intervención quirúrjica parece ser necesaria una combinación con drogas analgésicas. Cuando se incrementó la dosis de la droga (0,1–0,4 mg kg^{-1}) se observó con carácter concomitante un incremento lineal de la concentración del plasma y del periodo de actividad. La anestesia podría prolongarse mediante inyecciones adicionales o mediante infusión continua. Cada una de las inyecciones adicionales produjo un nuevo incremento de la concentración, de poca duración, junto con un incremento del grado de hipnosis. La infusión produjo tan sólo un incremento moderado de la concentración de plasma, al tiempo que la profundidad del sueño durante el periodo de infusión permaneció más o menos constante. Los cambios en el e.e.g. inducidos por la etomidata fueron similares a los producidos por los barbitúricos y demás anestésicos intravenosos.

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INFLUENCE OF MEDICATION, PAIN AND PROGRESS IN LABOUR ON PLASMA β-ENDORPHIN-LIKE IMMUNOREACTIVITY

T. A. THOMAS, J. E. FLETCHER AND R. G. HILL

SUMMARY

Plasma β-endorphin-like immunoreactivity (β-ELI) was measured at intervals during labour in 42 patients. An increase in β-ELI occurred during labour and increased to a maximum during the second stage. The increase in β-ELI paralleled dilatation of the cervix. A correlation existed between the duration of labour and second stage β-ELI in patients with labours of more than 4 h duration. Analgesic drugs were associated with changes in β-ELI. The patients who received Entonox had greater plasma β-ELI concentrations than those who received pethidine. A significant difference in the second stage β-ELI existed between those who received only Entonox and those who received only pethidine. Induction and augmentation of labour were also associated with differences in β-ELI. Patients in spontaneous labour had significantly lower β-ELI than patients who had either artificial rupture of membranes or Syntocinon augmentation of labour.

Substances with morphine-like properties which occur naturally in the body are referred to as endogenous opioids. Most of these substances are peptides and they have now been found in the brain, pituitary, adrenal, blood, urine and milk (Leong Way, 1980). The opioid which we have studied, β-endorphin, is a large peptide containing 31 amino acids. It is widely believed to be one of the neuromodulatory substances involved in the control of pain perception and there are well described neuronal pathways in which β-endorphin has been identified (Bloom et al., 1978). It has produced analgesia to experimental noxious stimuli when injected into the ventricle of rats (Bradbury et al., 1976) and recently has been injected intrathecally to produce analgesia in intractable pain syndromes (Oyama, Jin et al., 1980) and labour (Oyama, Matsuki et al., 1980).

β-Endorphin is also present within the pituitary (Li and Chung, 1976) and is thought to be released into the circulation during periods of stress (Fraioli et al., 1980).

Pain, stress and marked changes in pituitary secretion occur during labour. A reduction in the appreciation of labour pain during the second stage is said to occur (Selwyn-Crawford, 1972). This is a period in labour when pituitary secretion of hormones is at a maximum (Swaab and Boer, 1979). Accordingly we have studied the changing plasma β-endorphin-like immunoreactivity (β-ELI) during labour and have attempted to correlate β-ELI with various events and their progress in labour. Preliminary reports of some of these results have been made previously (Fletcher, Hill and Thomas, 1980; Fletcher, Thomas and Hill, 1980).

METHODS

The study was carried out in 42 patients with singleton pregnancies and who were between 17 and 37 yr of age. All of them gave their informed consent for blood samples to be taken and for pain scores to be obtained during labour. All pregnancies were between 38 and 43 weeks gestation, 22 patients were primiparous and 20 were multiparous. Spontaneous onset of labour occurred in 18 patients and in the remaining 24 labour was induced with Prostin pessaries or artificial rupture of the membranes. Cervical dilatation was assessed during routine vaginal examination by the attending midwife. Patients were excluded who, before labour, were receiving therapy likely to interfere with our assays or influence pituitary secretion (e.g. corticosteroids). Patients with endocrine abnormalities (e.g. diabetes) and those receiving anti-hypertensive therapy or sedatives for pre-eclampsia were also excluded. Seven analgesic regimens were identified. These were: no analgesia; pethidine only; Entonox only; pethidine and Entonox; pethidine, Entonox and extradural block; Entonox and extradural. A total of seven patients received pethidine and the remaining 35 received no analgesia, Entonox or an extradural, or both.

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TABLE I. *Blood sampling times*

	Sample	Time of sampling
(1)	Pre-labour control	(a) Induced labours: approx 12 h before induction (b) Spontaneous labours: approx. 36th week of pregnancy
(2)	Early first stage	Dilatation of cervix less than 5 cm
(3)	Late first stage	Dilatation of cervix greater than 5 cm
(4)	Second stage	Within the 30 min preceding delivery
(5)	Post partum	After completion of third stage and within 2 h of delivery
(6)	Cord	From a placental umbilical vessel after completion of third stage

Five-millilitre blood samples were taken from an antecubital vein at the times indicated in table I. Five maternal samples and one cord blood sample were taken and placed in lithium heparin tubes. They were spun in a refrigerated centrifuge within 15 min of being taken and the supernatant plasma was stored at −20 °C. Peptides were extracted from plasma and assayed using the method described by Csontos and others (1979), which was modified to deal with 2-ml sample volumes. The samples were mixed with silicic acid (100 mg) which adsorbed the peptides and the resulting silicic acid–peptide complex was washed twice with distilled water (2 × 2 ml). Peptides were then desorbed from silicic acid with a hydrochloric acid 0.1 mol litre^{-1} : acetone (80:20 v/v) mixture 3 ml and the solvent mixture evaporated with nitrogen. The residue was dissolved in radioimmunoassay buffer 0.5 ml and the extract was stored at −20 °C. Assay was performed using the New England Nuclear Radioimmunoassay Kit (^{125}I) for β-endorphin so our results are recorded as β-endorphin-like immunoreactivity (β-ELI). The extraction system we have used is not specific for β-endorphin. It also concentrates similar molecules such as β-lipotropin (β-LPH) and the antibody in the NEN assay kit cross-reacts 50% with β-LPH. It has been variously estimated that 69–94% of total circulatory β-ELI is attributable to β-LPH, the remainder being β-endorphin (Bertagna et al., 1981). As only 50% β-LPH is likely to be detected in the NEN assay system, this would suggest between 12 and 47% of the concentrations we estimate are attributable to β-endorphin alone, an estimate confirmed by other workers (Genazzini, Facchinetti and Parrini, 1981).

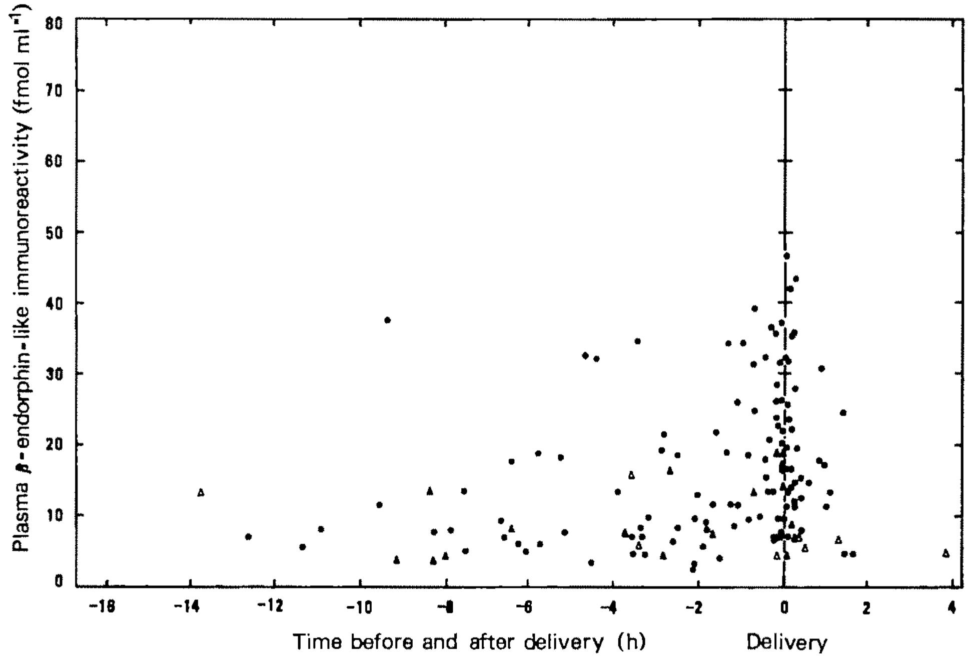

FIG. 1. Plasma β-endorphin-like immunoreactivity concentration during labour in relation to time before and after delivery. ● Patients who did not receive pethidine; △ patients who did receive pethidine.

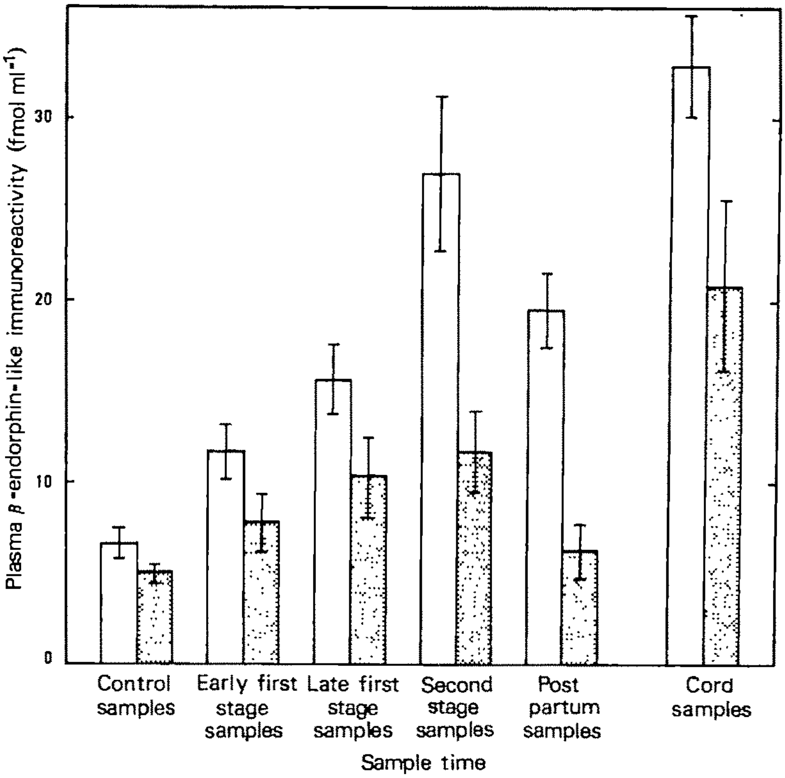

FIG. 2. Plasma β-endorphin-like immunoreactivity concentration at each sampling interval during labour, mean values and SEM. □Patients who did not receive pethidine; □patients who did receive pethidine.

Pain scores were obtained immediately before or after each blood sample. Patients used a linear analogue pain scale to assess the severity of their pain at that time. The left-hand end of the line represented no pain (0%) and the right-hand end the worst pain imaginable (100%). The use of the scale was explained to patients when the control sample was taken.

RESULTS

β-ELI and progress in labour

Considerable variations in plasma β-ELI occurred, both within and between patients during labour.

An increase in assayed plasma concentrations of β-ELI was detected as labour progressed in all patients (fig. 1), which was more clearly seen when mean β-ELI was estimated for each sampling time (fig. 2).

β-ELI was also recorded in relation to the stage of labour as judged by cervical dilatation. A significant increase in β-ELI occurred as the cervix dilated except in patients who received pethidine (fig. 3). The latter group had uniformly small values of β-ELI throughout early labour. The pethidine group are identified separately in figures 1–3 because of the possibility of feedback by this opiate on β-endorphin release from the pituitary.

Duration of labour, as judged by the attending midwife, in patients who did not receive pethidine, was plotted against β-ELI recorded in the second stage of labour to give some idea of the response time and capacity for the secretion of β-endorphin during labour. A correlation ($r = 0.81$) exists between the plasma β-ELI in second stage and the duration of labour in patients with labours in excess of 4 h duration (fig. 4). Not all patients follow a linear relationship. Two patients (fig. 4) had long labours, but showed only a small increase in β-ELI. Both of these patients were exceptionally anxious. One of them was receiving a diuretic (bendrofluazide), a nasal decongestant (Dimotapp LA) containing two sympathomimetics and an antihistamine. The other patient was so apprehensive that she was difficult to examine vaginally and was stated to have a low pain threshold before labour began.

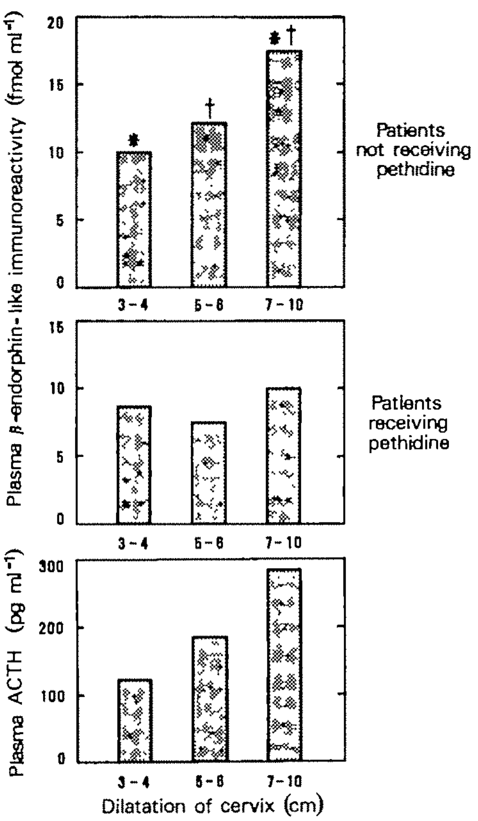

FIG. 3. Mean plasma β-endorphin-like immunoreactivity and ACTH concentrations related to cervical dilatation, during the first stage of labour. ACTH results from Kauppila, Tuimala and Haapalahti (1974). *†Significantly different groups (Mann-Whitney U test. $P<0.05$).

We have therefore excluded these two patients from the calculations in figure 4. The six patients with labours of less than 4 h duration showed a very rapid increase in β-ELI and five of them achieved high plasma concentrations in the second stage.

β-ELI and pain in labour

No correlation existed between β-ELI and pain scores at any stage of labour. Patients did, however, seem to have one of three types of β-ELI response patterns. The first response pattern showed a small increase (less than 2.5 times above control). The second response pattern showed a rather greater increase (2.5–4.5 times control) and the third response pattern showed the greatest change (more than 4.5 times control). No significant difference was detectable between the pain scores of the groups. An increase in pain scores occurred as labour progressed (table II).

TABLE II. *Median per cent pain scores recorded at blood sampling times during labour*

Stage of labour	Early first stage	Late first stage	Second stage	Post partum stage
Number of patients	39	37	38	38
Median per cent pain score	20	59	80	9.5

β-ELI and medication

The number of blood samples assayed in first and second stages of labour and their distribution between the analgesic regimens were recorded (table III).

Several differences were apparent in late first- and second-stage results (fig. 5). The group of patients who received pethidine had lower plasma β-ELI than the group of patients who received Entonox. The difference between the Entonox only and pethidine only groups in second stage was considerable ($P<0.05$, Mann–Whitney U test). This difference between groups existed throughout labour but was greatest during the second stage.

Patients were also grouped according to the method of induction or augmentation of labour (table IV). Mean β-ELI concentrations were recorded for each group (fig. 6). The i.v. infusion of oxytocin (Syntocinon), vaginal insertion of Prostin pessaries and the simple mechanical stimulus of artificial rupture of membranes (ARM) were associated with changes in β-ELI. The patients in spontaneous labour had significantly lower ($P<0.05$) β-ELI in late first stage than those patients who had either ARM or Syntocinon augmentation of labour. Many patients did not present a simple picture because they received two or more of the oxytocin and induction procedures plus one or more analgesic regimens.

DISCUSSION

It is possible that pituitary secretion into the hypophyseal portal vessels is the mechanism of entry of β-endorphin into the central nervous system since such retrograde transport of hypophyseal hormones has been demonstrated (Oliver, Mical and Porter, 1977). Excessive secretion of β-endorphin in response to pain and stress may be associated with "spill-over" of β-endorphin into the systemic circulation such that plasma concentrations would be an indicator if not a measure of central nervous system events.

Plasma β-ELI increased through labour in the

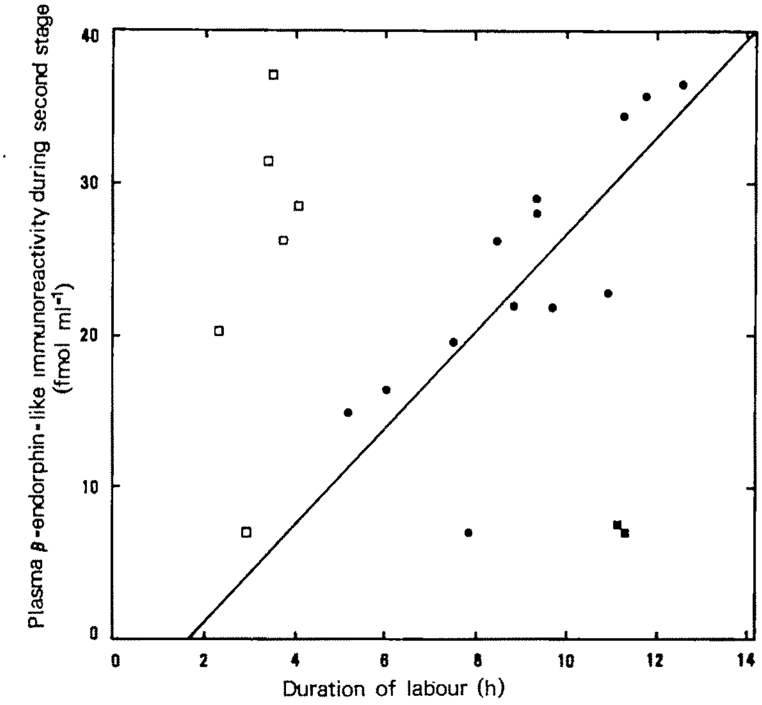

FIG. 4. Relationship between plasma β-ELI in second stage and duration of labour in patients who did not receive pethidine. □Patients with labour less than 4 h duration; ●■patients with labours of greater than 4 h duration; ●patients included in regression line calculations; ■patients excluded from regression line calculations for reasons given in the text. Slope of regression line 0.053 ± 0.026; $r = 0.81$; $P < 0.001$.

patients we have studied and this finding has been reported by other workers (Akil et al., 1979; Csontos et al., 1979). The change may be a response to stress, may be specifically related to pain perception or may have a totally different role. The correlation between plasma concentrations of pituitary–adrenal axis hormones and cervical dilatation (Kauppila, Tuimala and Haapalahti, 1974) may be indicative of a stress response. β-ELI may play a role in this response and our results indicate that the increase in plasma β-ELI parallels that of plasma ACTH previously measured in experiments on stressed animals (Guillemin et al., 1977).

Because of the opioid nature of β-endorphin it

TABLE III. *Number of patients and mean β-ELI concentrations in each analgesic regimen group. * "Total" does not reflect the total number of patients in the study, as a complete set of blood samples was not obtained from all patients*

	Early first stage		Late first stage		Second stage	
Analgesics received before blood sampling	Number of patients	Mean plasma β-ELI (fmol ml⁻¹)	Number of patients	Mean plasma β-ELI (fmol ml⁻¹)	Number of patients	Mean plasma β-ELI (fmol ml⁻¹)
None	22	9.2	6	8.1	1	7.0
Pethidine only	2	10.6	3	9.1	3	10.9
Entonox only	7	12.1	11	19.3	14	27.6
Extradural only	2	12.6	6	17.4	3	20.9
Pethidine + Entonox	3	8.5	3	13.5	3	15.1
Pethidine, Entonox + extradural	—	—	1	4.1	1	4.1
Entonox + extradural	1	37.8	7	11.1	6	21.5
Total*	37		37		31	

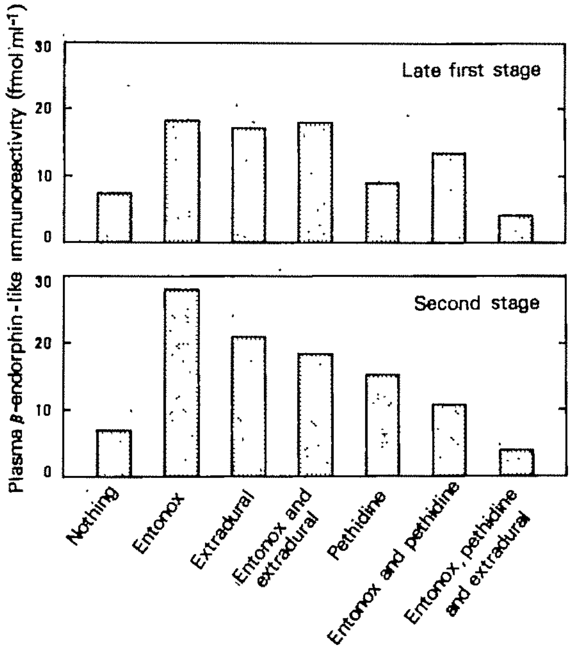

FIG. 5. Plasma β-endorphin-like immunoreactivity concentration and method of analgesia. Mean values.

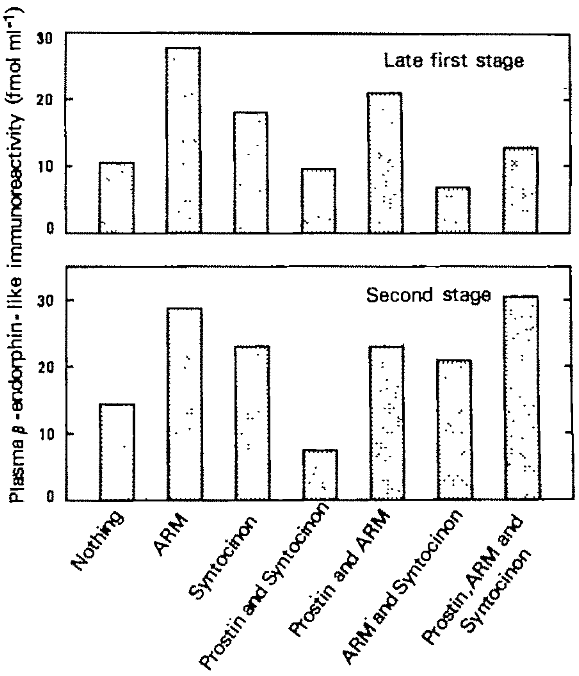

FIG. 6. Plasma β-endorphin-like immunoreactivity concentration and method of induction. Mean values. Patients not receiving pethidine.

might be expected that a correlation would exist between β-ELI and pain scores, but we have found no significant relationship linking them.

We have found a relationship between β-ELI and different methods of analgesia. In the patients studied, Entonox was associated with a greater increase in β-ELI than other forms of analgesia. It has been shown that nitrous oxide analgesia is antagonized by naloxone (Gillman, Kok and Lichtigfeld, 1980) and our results indicate that administration of nitrous oxide during labour is accompanied by β-endorphin release into the blood stream. Large concentrations of plasma β-endorphin following the administration of Entonox may be an indication of the mechanism of analgesic action of nitrous oxide.

Pethidine and extradural blocks were both as-

TABLE IV. *Number of patients and mean β-ELI concentrations in each induction regimen group. * "Total" does not reflect the total number of patients in the study, as a complete set of blood samples was not obtained from all patients*

	Early first stage		Late first stage		Second stage	
Induction agents received before blood sampling	Number of patients	Mean plasma β-ELI (fmol ml^{-1})	Number of patients	Mean plasma β-ELI (fmol ml^{-1})	Number of patients	Mean plasma β-ELI (fmol ml^{-1})
None	8	14.1	5	11.0	2	14.4
ARM	2	12.6	3	27.7	3	28.8
Syntocinon	—	—	2	18.2	2	23.1
Prostin	3	7.1	—	—	—	—
Prostin + Syntocinon	1	13.5	1	9.8	1	7.3
Prostin + ARM	9	10.2	8	21.5	5	23.0
ARM + Syntocinon	2	6.3	2	7.1	4	20.9
Prostin + ARM + Syntocinon	5	19.5	9	12.0	7	30.4
Total*	30		30		24	

sociated with lower levels of β-ELI in our patients. It is tempting to suggest that the low activity measured following administration of pethidine indicate a negative-feedback effect of this opiate on pituitary secretion of β-endorphin. The low levels that we have found after extradural analgesia with bupivacaine cannot be accounted for by the same hypothesis. It has been postulated that neurogenic blockade by extradural local anaesthetic agents interrupts the pathways responsible for mediating the afferent limb of the endocrine metabolic reflex during surgery (Hagen, Brandt and Kehlet, 1980). We believe that the removal of the pain appreciation and stress of labour reflected by lower plasma cortisol concentrations (Maltau, Eielsen and Stokke, 1979) and small acid–base changes (Pearson and Davies, 1974), may be the reason for the low β-ELI values found in patients receiving extradurals. The absence of stress responses from higher centres in the central nervous system would complement a neurogenic block of afferent pathways in stress response reflexes.

The suggestion that different pain levels are responsible for the association between β-ELI and methods of analgesia is not supported by our results as we found no correlation between pain scores and β-ELI in any group of patients nor any correlation of pain scores and method of analgesia. The greatest pain scores were commonly recorded by patients in the second stage of labour and this result contradicts the claim that second stage is the least painful part of a woman's labour. Peripheral events do have an effect on central processes, however. The influence of ARM on circulating β-ELI is an example of this link as ARM inevitably results in vaginal and cervical stimulation. The cervix is richly innervated with pain receptors and is arguably the origin of much of the pain in labour, so early stimulus of this site may result in earlier and greater increases in β-ELI. Vaginal distension has been shown in rats to produce analgesia which is reduced by naloxone (Hill and Ayliffe, 1981) and we suggest that a direct cause-and-effect relationship exists between ARM and an increase in plasma β-ELI produced as part of an endogenous analgesic system.

Before further investigation of the role of plasma endogenous opioids in pregnancy and labour is possible, more information must be obtained as to the absolute identity of these circulatory β-endorphin-like peptides. In order to overcome the problem of non-specificity of the antiserum and in an attempt to improve sensitivity, work is currently in progress both to develop a better radioimmunoassay and to fractionate plasma extracts using high-performance liquid chromatography. It is hoped that these methods will aid our identification of the opioid peptides and their role in pregnancy and labour.

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INFLUENCE DE LA THERAPEUTIQUE, DE LA DOULEUR ET DE L'AVANCEMENT DU TRAVAIL SUR L'IMMUNOREACTIVITE DE TYPE BETA-ENDORPHINE DU PLASMA

RESUME

L'immunoréactivité plasmatique de type β-endorphine (β-ELI) a été mesurée à intervalles réguliers au cours du travail chez 42 patientes. Une augmentation de β-ELI apparaissait au cours du travail et augmentait pour atteindre un maximum pendant la deuxième phase. L'élévation de β-ELI était parallèle à la dilatation du col. Il existait une correlation entre la durée du travail et la β-ELI au cours de la deuxième phase chez les patientes dont le travail durait plus de 4 h. L'administration d'analgésiques correspondait à des modifications de β-ELI. La β-ELI plasmatique des patientes qui recevaient de l'Entonox était significativement plus importante que celle des patientes qui recevaient de la pethidine. Il existait une différence significative dans la β-ELI de la deuxième phase chez les patientes qui ne recevaient que de l'Entonox par rapport à celles qui ne recevaient que de la pethidine. Le déclenchement et l'accélération du travail s'accompagnait aussi de différences de β-ELI. Les patientes avec un travail spontané avaient des β-ELI significativement plus basses que celles dont le travail était accéléré par la rupture artificielle des membranes ou le Syntocinon.

DER EINFLUß VON MEDIKAMENTATION, SCHMERZ UND WEHENTÄTIGKEIT AUF DIE PLASMA β-ENDORPHINÄHNLICHE IMMUNOREAKTIVITÄT

ZUSAMMENFASSUNG

Eine Plasma β-endorphinähnliche Immunoreaktivität (β-EI) wurde bei 42 Patientinnen in bestimmten Abständen unter der Geburt gemessen. Die Plasma β-EI stieg mit Einsetzen der Wehen an und erreichte in der Austreibungsphase den höchsten Wert. Die Zunahme der β-EI im Plasma lief parallel mit der Eröffnung des Muttermundes. Eine Korrelation bestand auch zwischen der Dauer der Geburt und den in der Austreibungsphase gemessenen β-EI-Werten wenn die Geburt mehr als 4 Stunden dauerte. Analgetika veränderten die Plasma β-EI, und zwar konnten wir nach Entonox-Gabe höhere Plasma β-EI-Konzentrationen messen als nach Pethidin-Gabe. Ein signifikanter Unterschied der β-EI-Konzentrationen in der Austreibungsphase bestand zwischen den Patientinnen, die nur Entonox und jenen Patientinnen, die nur Pethidin erhalten hatten. In der Einleitungsphase waren ebenfalls unterschiedliche β-EI-Werte meßbar. Patientinnen mit Spontangeburt hatten signifikant niedrigere Plasma β-EI-Konzentrationen als Patientinnen, deren Geburt mit ARM oder Syntocinon eingeleitet wurde.

INFLUENCIA DE LA MEDICACION, DEL DOLOR Y DEL PROGRESO DEL PARTO ANALIZADA EN FUNCION DE LA INMUNOREACTIVIDAD DEL TIPO β-ENDORFIN DEL PLASMA

SUMARIO

Se midió la inmunoreactividad de tipo β-endorfin del plasma (β-ITE) a diversos intervalos del parto en 42 pacientes. Durante el parto se produjo un incremento de la β-ITE, alcanzando este incremento su punto álgido durante la segunda fase. El incremento de la β-ITE fue paralelo a la dilatación del cervix. En aquellas pacientes cuyo parto duró más de 4 horas, tuvo lugar una correlación entre la duración de dicho parto y la β-ITE de la segunda fase. Las drogas analgésicas vinieron asociadas con cambios en la β-ITE. Las pacientes que recibieron Entonox presentaron mayores concentraciones de β-ITE en el plasma que aquellas que recibieron petidina. Hubo una diferencia significativa en la β-ITE de la segunda fase entre aquellas pacientes que recibieron Entonox solamente y aquellas otros que recibieron tan sólo petidina. La inducción y el incremento de la intensidad del parto vinieron también asociados con diferencias en la β-ITE. Las pacientes cuyo parto fue expontáneo presentaron una β-ITE significativamente inferior que las pacientes a los que se les practico la ruptura artificial de las membranas o la aceleración del proceso de parto mediante Syntocinon.

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A CONTROLLED TRIAL OF EXTRADURAL FENTANYL IN LABOUR

D. M. JUSTINS, D. FRANCIS, P. G. HOULTON AND F. REYNOLDS

SUMMARY

In a double-blind trial carried out on patients in the first stage of labour, either fentanyl 80 μg ($n = 35$) or physiological saline ($n = 33$) was added to the test dose of bupivacaine and administered extradurally. Thereafter analgesia was maintained as necessary with 0.5% bupivacaine alone. Supplementary bupivacaine (a further dose within 1 h) was required to produce satisfactory analgesia in eight patients in the fentanyl group and in 26 patients in the control group. Analgesia was more rapid in onset and more complete in the fentanyl group, and the duration from first dose to first top-up was 2.36 h, compared with 1.66 h (supplements notwithstanding) in the control group. No serious side-effects were encountered in either group, although eight patients in the fentanyl group experienced mild itching, compared with one in the control group.

Extradural blockade using local anaesthetic agents relieves pain in labour effectively. However, side-effects may result from the non-selective nature of the nerve block. Extradural opiates act on receptors in the substantia gelatinosa of the spinal cord (Kitahata and Collins, 1981) and block pain pathways selectively. This investigation was designed to assess whether small doses of an opiate, administered extradurally in obstetric patients, would decrease the dose of local anaesthetic drug required.

Following initial success with fentanyl in labour (Francis, Justins and Reynolds, 1981), the present double-blind trial tested the effect of a single injection of fentanyl given to the extradural space with the bupivacaine test dose in early labour. By this means there was no delay in providing pain relief, despite the use of saline controls.

PATIENTS AND METHODS

All patients requiring extradural analgesia while in the first stage of labour and when one of the authors was present, were included in the trial. Any patient who had received two or more doses of narcotic analgesic systemically and any in whom the second stage was imminent were excluded.

An extradural catheter was inserted via the L2/3 interspace. The contents of a randomly-coded ampoule containing either saline or fentanyl 100 μg were mixed with 0.5% bupivacaine 3 ml without adrenaline and injected through a 1-ml Millipore filter with the patient supine. This first dose was therefore 4 ml of 0.3% bupivacaine either alone or containing fentanyl 80 μg.

The maternal circulation was pre-loaded with Hartmann's solution and the fetal heart pattern and maternal arterial pressure were monitored for 30 min following this first dose. If by 10 min pain had not diminished or there was residual unilateral or perineal pain, supplementary doses of 0.5% bupivacaine were given in the appropriate posture to relieve pain. The return of painful uterine contractions was treated in the conventional manner with 0.5% bupivacaine alone.

Pain was measured using a 10-cm visual analogue scale on four occasions:

(i) the pain of uterine contractions immediately preceding the first dose;
(ii) the pain of the extradural procedure, to give a measure of the patient's sensitivity to pain;
(iii) the pain of the first uterine contraction after 8 min from the first dose. This was to record the pain score as nearly as possible at 10 min, given the unpredictability of uterine contractions;
(iv) the pain of uterine contraction at 30 min.

Where possible the time of the first painless contraction was recorded, as was the frequency of side-effects. Findings were analysed by fitting linear models to the data using the statistical package GLIM (Baker and Nelder, 1978). Significance of differences was detected using Student's *t* test or, for frequency data, Yates' modification of the χ^2 test.

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RESULTS

On two occasions a coded ampoule was drawn up and subsequently discarded because the patient was found to be in the second stage. In all, 68 patients took part in the trial (table I). Unfortunately, when the results were decoded, an imbalance in parity between the groups was revealed, the lower mean age in the fentanyl group being a reflection of this. (A continuation of the trial even to double the numbers would have been unlikely to counterbalance this chance event.) The two groups were comparable in other respects which are relevant to the trial, namely pain sensitivity, pain score and degree of cervical dilatation at the time of the first extradural dose (table I).

TABLE I. *Patient data (mean ± SEM)*

	Control group	Fentanyl group
n	33	35
Age (yr)	28.0 ± 0.8	25.9 ± 0.9
Parity (numbers) Primipara	20	29
Multipara	13	6
Cervical dilatation before blockade (cm)	2.9 ± 0.2	2.9 ± 0.2
Pain score before blockade (cm)	6.9 ± 0.3	6.4 ± 0.4
Pain score for extradural procedure (cm)	1.7 ± 0.3	2.0 ± 0.3

Supplements (further doses of bupivacaine within the first hour)

Seventy-nine per cent of patients in the control group required supplements and only 23% in the fentanyl group (table II). This difference between the two groups is significant ($\chi^2 = 19.1$; $P \leqslant 0.001$). Supplements were given 7–37 min after the first dose in the control group and 10–54 min after the first dose in the fentanyl group. Of the eight patients in the fentanyl group who received supplements, four had only unilateral pain and two perineal pain after the first dose. Only one patient needed more than one supplement, compared with seven in the control group. Of the patients requiring supplements, the total supplement volume of 0.5% bupivacaine (mean ± SEM) in the control group was 5.19 ± 0.36 ml and in the fentanyl group, 4.56 ± 0.56 ml. The mean total dose for all the control patients was equivalent to 6.09 ml of 0.5% bupivacaine which approximates closely to our standard first dose (6 ml) in the average patient.

TABLE II. *Numbers of patients needing supplements*

	Control group ($n = 33$)	Fentanyl group ($n = 35$)
No supplement	7 (21.2%)	27 (77.1%)
Supplement	26 (78.8%)	8 (22.9%)
Supine	10	2
Lateral	12	4
Sitting	4	2
More than one dose	7 (21.2%)	1 (2.9%)

Pain scores

The changes in pain scores (fig. 1) in the two groups are presented in terms of a decrease in pain from the initial score, 0 representing no change in pain and −100% no pain at all. The greater decrease in pain in the fentanyl group at 10 min was expected. However, although by 30 min most of the patients in the control group had received supplements of bupivacaine, pain relief was still better in the fentanyl group.

Time to first painless contraction

Figure 2 shows the cumulative numbers of patients in each group experiencing painless contractions in each 5-min period following the first dose. By 20 min this included 71% of the fentanyl patients but only 27% of the control group. The mean time to

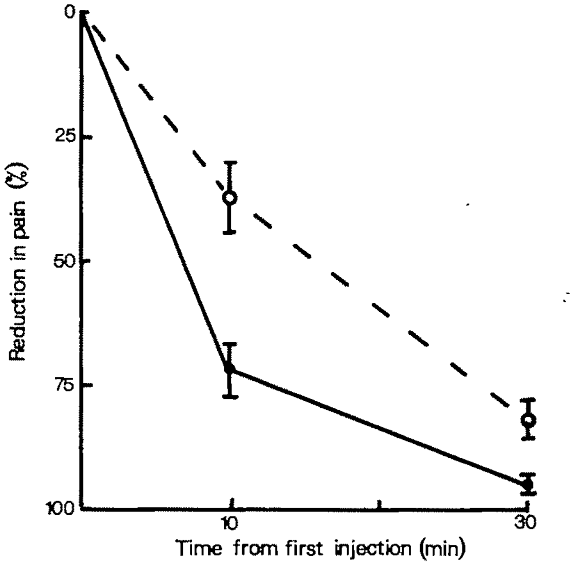

FIG. 1. Change in pain score after the first extradural injection in the fentanyl group (●——●) and in the control group (○---○). Vertical bars represent standard errors. The difference between the two groups is significant at 10 min ($P < 0.001$) and at 30 min ($P < 0.01$).

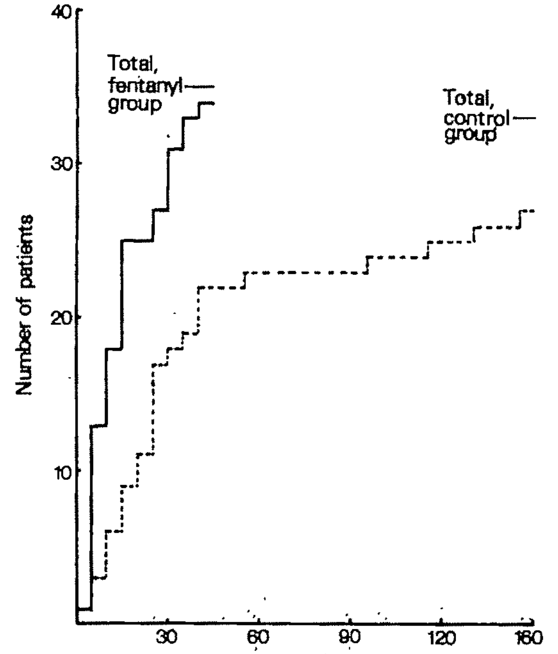

FIG. 2. Cumulative numbers of patients experiencing pain-free contractions in the fentanyl (——) and in the control groups (---).

painless contraction was 18 min in the fentanyl group and 59 min in the controls.

Duration of analgesia

In eight patients delivery occurred before a top-up (defined as a dose of bupivacaine given more than 1 h after the first dose) was needed. The duration of action from first dose to first top-up is given in table III for the remaining 60 patients. The duration of analgesia in the fentanyl group was significantly longer than in the control group, despite the fact that 21 of the 28 controls received supplements of bupivacaine between the first dose and the first top-up. Although seven controls required no supplement to produce analgesia, the mean duration of action in these patients was only 1.40 ± 0.08 h, whereas fentanyl without supplements was effective for 2.38 ± 0.15 h. Eight fentanyl patients in whom the segmental level of analgesia to pinprick was very low or asymmetrical still experienced satisfactory and prolonged analgesia.

TABLE III. *Duration of analgesia (h) first dose to first top-up*

	Control group (mean ± SEM)	Fentanyl group (mean ± SEM)	*P*
All patients	1.66 ± 0.06 (n = 28)	2.36 ± 0.14 (n = 32)	<0.001
Patients requiring supplements	1.75 ± 0.23 (n = 21)	2.25 ± 0.49 (n = 6)	n.s.
Patients requiring no supplement	1.40 ± 0.08 (n = 7)	2.38 ± 0.15 (n = 26)	<0.001

Total dose of bupivacaine

The total dose of bupivacaine was slightly greater in the control group (table IV), but as the labours were longer in the fentanyl group, the dose rate of bupivacaine (mg h^{-1}) was significantly greater in the controls. This difference could be accounted for solely by the increase in the number of supplements in the control group.

TABLE IV. *Total dose of 0.5% bupivacaine (ml) (mean ± SEM)*

	Control group	Fentanyl group	*P*
Primipara	24.7 ± 3.5	20.7 ± 2.4	n.s.
Multipara	17.3 ± 3.8	14.5 ± 3.4	
All patients	21.8 ± 2.6	19.6 ± 2.1	
Dose rate (ml h^{-1})	4.2 ± 0.52	2.9 ± 0.29	<0.05

Side-effects

Hypotension, as defined by a decrease in systolic pressure of more than 20%, occurred in one patient in the control group (decrease from 150 to 120 mm Hg) and in five patients in the fentanyl group, all of whom experienced complete relief of pain. In only one patient did the systolic pressure decrease briefly to less than 90 mm Hg.

Other side-effects are shown in table V. The only significant difference between the two groups was in the frequency of itching, which was not a spontaneous complaint and was usually confined to the area of analgesia.

TABLE V. *Frequency of side-effects (other than hypotension).* *$\chi^2 = 4.2$; P<0.05

	Control group (n = 33)	Fentanyl group (n = 35)
Nausea and vomiting	2	2
Itching	1	8*
Leg weakness (1st hour)	2	1
Post-partum		
Bladder dysfunction	2	1
Headache	nil	nil

Type of delivery

There were 54% normal deliveries, with no significant difference between the two groups.

The baby

No changes in fetal heart pattern occurred in association with any of the extradural blocks and there were no perinatal deaths. The Apgar scores at 1 and 5 min were: controls, 7.9 ± 0.2 and 9.4 ± 0.2 respectively; fentanyl, 7.4 ± 0.4 and 9.2 ± 0.2 respectively.

DISCUSSION

Despite the success of spinal opiates in relieving pain after operation (Bromage, Camporesi and Chestnut, 1980; Chayen, Rudick and Borvine, 1980; Magora et al., 1980; Weddel and Ritter, 1981) and certain types of chronic pain, the method has not proved as valuable in obstetrics. Results have been variable, with wide disparity between reported effects of the same drug and technique in different centres. Morphine has been given in labour both intrathecally (Scott et al., 1980; Baraka, Noueihid and Hajj, 1981) and extradurally (Booker, Bryson and Beddard, 1980; Chayen, Rudick and Borvine, 1980; Husemeyer, O'Connor and Davenport, 1980; Magora et al., 1980; Crawford, 1981; Writer, James and Wheeler, 1981) while Perriss (1979, 1980) has reported on pethidine, phenoperidine and fentanyl administered into the extradural space. The disappointing effects of the narcotic alone may be a consequence of the pain pathways involved in labour. Most uterine pain is conducted by Aδ fibres, some of which bypass opiate receptors in the substantia gelatinosa (Bowsher, 1978). Our own experience (Francis, Justins and Reynolds, 1981) and that of others (Booker, Bryson and Beddard, 1980; Perriss, 1980), demonstrates that on occasions the narcotic alone will work very well in early labour but the result is not predictable.

Fentanyl was chosen because of its high lipid solubility and high receptor affinity. The molecule has no phenolic or alcoholic hydroxyl groups and has a long side-chain on the amine nitrogen conferring increased lipid solubility, analogous to the effect seen with local anaesthetic molecules. Morphine, the most commonly used agent, has three polar groups, one basic and two weakly acidic, and has a low lipid solubility resulting in slow lipid membrane penetration (Oldendorf et al., 1972). Morphine has been effective when given intrathecally in obstetrics (Scott et al., 1980; Baraka, Noueihid and Hajj, 1981) thus bypassing the dura, and after extradural injection in certain other non-obstetric pains (Bromage, Camporesi and Chestnut, 1980; Chayen, Rudick and Borvine, 1980) where the slow onset time and less predictable action are not a disadvantage. Fentanyl is much less hydrophilic than morphine so is less likely to remain in the cerebrospinal fluid in concentrations capable of producing delayed respiratory depression. This has been a problem with morphine and pethidine (Glynn et al., 1979; Scott and McClure, 1979; Reiz and Westberg, 1980) but not with fentanyl even when used in an infusion (Bailey and Smith, 1980).

Although our original intention had been to include a group receiving fentanyl i.m., this was judged unethical for the following reasons. First, the expectation of the patients was for extradural analgesia. Second, many patients select this method of pain relief to avoid an i.m. injection and, if included, each patient would have received such an injection. However, few would expect to achieve 2.5 h of obstetric analgesia from fentanyl 80 μg given systemically. Wolfe and Davies (1980) showed virtually insignificant plasma concentrations following the extradural administration of fentanyl 0.1 mg following Caesarean section. Measurements of plasma and cerebrospinal fluid concentrations after extradural pethidine showed that the onset of analgesia coincided with high cerebrospinal fluid concentrations, well before analgesic plasma concentrations were attained (Cousins, Mather et al., 1979). The analgesic effect of extradural morphine correlated poorly with serum morphine concentrations (Weddel and Ritter, 1981). It has been postulated that extradural opiates may produce analgesia by a central action after transport to the brain in the cerebrospinal fluid (Crawford, 1980) or via venous plexuses. However, regional analgesia has been demonstrated in rats (Yaksh and Rudy, 1976) and man (Torda et al., 1980) and we ourselves were convinced of the segmental quality of the analgesia obtained with fentanyl. Diffusion of the drug into the cerebrospinal fluid from the extradural space and subsequent uptake into the dorsal horn has been suggested by Bromage, Camporesi and Chestnut (1980) as a mechanism of transport. Most workers have injected the opiates in large carrier volumes to obtain spread to the appropriate spinal cord segments, which for labour pain (T11 and 12) would be at the level of thoracic vertebrae 8 and 9. We found that, using only 4 ml injected at the lumbar 2/3 interspace, the distribution of effect closely resembled that following bupivacaine given at the same site, which often leaves the sacral segments unaffected. It is difficult to reconcile this regional effect with the suggested diffusion through cerebrospinal fluid which should result in an effect on *lower* spinal segments. Axonal transmission from the extradural space to the dorsal horn lamina is an alternative explanation (Iversen, 1979).

Local anaesthetic agents have a shorter duration of action in labour than in other types of pain and the same pattern occurs with opiates. We have found that after Caesarean section fentanyl produced analgesia lasting about 4 h (Houlton and Reynolds, 1981). Wolfe and Nicholas (1979) demonstrated a duration of action of 200–240 min following Caesarean section. Bromage, Camporesi and Chestnut (1980) reported a mean duration of 16.7 h for extradural morphine in postoperative pain, yet the most favourable obstetric trial demonstrated a duration of analgesia of only 5.25 h (Booker, Bryson and Beddard, 1980).

The use of extradural fentanyl was free from serious complications and the only significant side-effect, itching, was mild and not unpleasant.

The five patients who exhibited systemic hypotension following fentanyl also experienced effective pain relief and Cousins, Glynn and colleagues (1979) reported similar transient hypotension in patients recovering from surgery following relief of pain using extradural pethidine. Cousins, Glynn and co-workers (1979), Bromage, Camporesi and Chestnut (1980) and Writer, James and Wheeler (1981) confirmed the absence of efferent sympathetic nerve block.

CONCLUSIONS

Fentanyl 80 μg given with the extradural test dose can produce complete analgesia in the first stage of labour and is significantly longer acting than bupivacaine alone.

Although the present study does not demonstrate an overall decrease in side-effects after using a single dose of fentanyl in unselected patients, we have found it a useful alternative to bupivacaine in three particular circumstances: before a difficult ARM in an apprehensive patient; for obstinate perineal pain in the first stage; when hypotension would be a serious hazard.

In the first two indications, the leg weakness which may result from a full sitting dose of bupivacaine is avoided at an early stage. In the third indication, fentanyl may be used successfully in specific patients in whom extradural bupivacaine has been associated with hypotension or disordered fetal heart pattern.

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UN ESSAI CONTROLE DU FENTANYL EN PERIDURALE AU COURS DU TRAVAIL

RESUME

Dans une étude en double aveugle pratiquée sur des patientes pendant la première phase de travail, 80 μg de fentanyl ($n = 35$) ou du chlorure de sodium à 9% ($n = 33$) ont été ajoutés à la dose test de bupivacaïne et administrés dans l'espace péridural. Par la suite, l'analgésie a été entretenue, si nécessaire, avec de la bupivacaïne à 0,5% seule. Pour avoir une analgésie satisfaisante, huit patientes du groupe fentanyl et 26 patientes du groupe témoin ont eu besoin d'une réinjection de bupivacaïne (dose rajoutée au bout de 1 h). L'analgésie était d'installation plus rapid et plus complète dans le groupe fentanyl, et le délai entre la première dose et le premier retour à l'état initial y était de 2,36 h, contre 1,66 h dans le groupe témoin (sans tenir compte des réinjections). Nous n'avons constaté aucun effet secondaire sérieux dans aucun des deux groupes, bien que huit patientes du groupe fentanyl se soient plaintes d'un léger prurit, qui n'est survenu qu'une fois dans le groupe témoin.

EINE KONTROLLIERTE STUDIE ÜBER EPIDURALE GABE VON FENTANYL IN DER GEBURTSHILFE

ZUSAMMENFASSUNG

In einem Doppelblindversuch, der bei den Eröffnungswehen in der Geburtshilfe durchgeführt wurde, erhielten die Patientinnen entweder Fentanyl 80 μg ($n = 35$) oder Kochsalz ($n = 33$) epidural zu der Testdosis von Bupivacain. Danach wurde die Analgesie bei Bedarf mit Bupivacain 0,5% aufrechterhalten. Zusätzliches Bupivacain (eine weitere Dosis innerhalb von 1 Stunden) war zur notwendigen Analgesie in der Fentanyl-Gruppe bei 8 Patientinnen und in der Kontroll-gruppe bei 26 Patientinnen notwendig. In der Fentanyl-Gruppe setzte die Analgesie schneller ein und war vollständiger als in der Kontrollgruppe und die Dauer der ersten Dosis in ihrer maximalen Analgesiewirkung betrug 2,36 h verglichen mit 1,66 h in der Kontrollgruppe. In keiner Gruppe traten ernsthafte Nebenwirkungen auf, lediglich 8 Patientinnen der Fentanyl-Gruppe und 1 Patientin der Kontrollgruppe verspürten leichtes Hautjucken.

PRUEBA CONTROLADA DE FENTANILO EXTRADURAL DURANTE EL PARTO

SUMARIO

Durante una prueba de doble anonimato efectuada en pacientes que se encontraban en la primera fase del parto, se añadieron bien 80 μg de fentanilo ($n = 35$) o una disolución salina de carácter sicológico ($n = 33$) a la bupivacaína, la cual se administró extraduralmente. La analgesia se mantuvo posteriormente con sólo bupivacaína al 0,5%, según las necesidades. Fue necesaria bupivacaína suplementaria (una dosis adicional en el periodo del 1 h) para producir la analgesia satisfactoria en ocho de las pacientes del grupo sometido a fentanilo y en veintiseis pacientes del grupo de control. La analgesia fue más rápida al principio y más completa en el grupo sometido a fentanilo, obteniéndose una duración de 2,36 h desde la primera dosis hasta el nivel máximo, en comparación con 1,66 h (a pesar de los suplementos) para el grupo de control. No se obtuvieron efectos secundarios graves en ninguno de los grupos, aunque ocho de las pacientes sufrieron escozores ligeros dentro del grupo de fentanilo en comparación con sólo una paciente en el grupo de control.

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EXTRADURAL PETHIDINE WITH AND WITHOUT ADRENALINE DURING LABOUR: WIDE VARIATION IN EFFECT

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SUMMARY

The pain-relieving effect of a single extradural dose of pethidine 25 mg with and without adrenaline was studied in 20 healthy women during labour. The study was open regarding the effects of pethidine but double-blind regarding the addition of adrenaline. In 14 of 19 women good or excellent analgesia was achieved for a period of 50–160 min. Pethidine with adrenaline 25 μg was not more effective than pethidine alone. Eight of the 14 women showed signs of regional analgesia to pin-prick and temperature discrimination. The patients had small (45–188 ng ml^{-1}) concentrations of pethidine in plasma. In eight patients the plasma concentrations of pethidine were maintained for at least 1.5 h. Extradural pethidine thus induces analgesia of short and variable duration. Repeated doses may be needed, resulting in accumulation of the drug in plasma with the risk of respiratory depression in mother or child.

Extradural analgesia with local anaesthetics is accepted as a reliable and safe method during labour (Moir, 1976; Bromage, 1978). However, even with segmental analgesia (Zador and Nilsson, 1974; Hollmén et al., 1977) the efficiency of uterine contractions in the first stage of labour is slightly decreased and weakness of the abdominal muscles and inhibition of the pushing reflex in the second stage of labour results in an increased number of outlet extractions (Willdeck-Lund, Lindmark and Nilsson, 1979). In uncontrolled studies small extradural doses of opiates gave long-lasting relief of postoperative and chronic pain with unimpaired muscular function (Bahar et al., 1979; Bromage, Camporesi and Chestnut, 1980; Graham, King and McCaughey, 1980).

This type of selective opiate-induced analgesia would be a more physiological way to relieve pain during labour. However, small doses of morphine (2–4 mg) in the extradural space have failed to provide sufficient analgesia during labour (Booker et al., 1980; Husemeyer, O'Connor and Davenport, 1980; Magora et al; 1980; Nybell-Lindahl et al., 1981). By virtue of its higher lipophilicity (Goodman and Gilman, 1975; Yaksh, 1981) pethidine might reach the spinal cord more rapidly than morphine. Addition of adrenaline might decrease the absorption of pethidine to the systemic circulation and thereby increase the local concentration of the drug.

This study was undertaken to investigate the analgesic effect and duration of a single extradural dose of pethidine 25 mg with and without adrenaline during the first stage of labour. Another aim was to study the relation between the analgesia and the plasma concentrations of pethidine.

METHODS

Twenty healthy women with normal pregnancies were studied. All patients were at term; 10 were nulliparous. The study was approved by the Department of Drugs of the National Board of Health and Welfare and by the ethics committee of the hospital. All patients gave their informed consent.

The extradural catheter was introduced when the cervix was dilated to 3–4 cm. Extradural puncture was performed by paramedian technique (Bonica, 1972) at the L2–L3 interspace and the catheter was introduced 2–3 cm.

The women were randomly allocated to one of two groups. Both groups were given a single dose of pethidine 25 mg in 5 ml of saline with or without adrenaline 5 μg ml^{-1}. Balanced saline solution 400–500 ml was administered prophylactically to prevent a decrease in arterial pressure. Systolic and diastolic arterial pressures and respiratory rates were monitored.

If adequate analgesia was not achieved within 30 min, 5 ml of 0.25% bupivacaine containing adrenaline 5 μg ml^{-1} was administered via the catheter.

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Pain relief was estimated with a 10-cm horizontal visual analogue scale (VAS) before and 20 min after the administration of pethidine or bupivacaine (Huskisson, 1974; Scott and Huskisson, 1976). An unused scale was shown on each occasion. The duration of analgesia was calculated as the time in minutes until the patient required additional analgesia consisting of bupivacaine 5 ml or until the time of delivery.

To determine the plasma concentrations of pethidine blood samples were taken before and 5, 15, 30, 60, 90 and 120 min after the administration of pethidine and thereafter hourly until delivery. Mixed blood from the umbilical cord was withdrawn immediately after birth. The samples were centrifuged within 30 min and the plasma was withdrawn and frozen at −20°C. Pethidine analyses in duplicate were carried out with mass fragmentography with deuterium-labelled pethidine as an internal standard. The limit of sensitivity of this method in 100-μlitre plasma samples is 5 ng ml^{-1} (G. Tomson and colleagues, in preparation).

Tests for discrimination of temperature, pinprick and sensation of heavy legs were carried out before and 20 min after the injection of pethidine or bupivacaine. The infants were assessed with Apgar scores at 1 and 5 min. Any sign of respiratory depression was monitored. All blocks and the assessment of the analgesic effect, the segmental distribution and the duration of analgesia were performed by the same senior anaesthetist.

Pethidine concentrations in plasma and percentage pain relief are given as median values.

RESULTS

Various degrees of pain relief were achieved at 20 min after administration of pethidine (fig. 1). Ten patients indicated 71–100% pain relief ("excellent analgesia"), four patients indicated 31–70% pain relief ("good analgesia") and five patients had 0–30% pain relief ("poor analgesia"). Seventy-four per cent of all patients thus indicated good or excellent analgesia. One patient who delivered her child before analgesia was achieved was excluded.

Median values of pain relief at 20 min in patients who received pethidine with and without adrenaline were 74% and 61% respectively. Patients with good or excellent pethidine analgesia noted an incipient analgesic effect after 5–10 min and fully established analgesia after 10–15 min.

In the group with excellent or good analgesia none of the patients required additional injections during the first 50 min (fig. 2). Six patients experienced pain relief lasting for more than 115 min and in three patients the effect remained at delivery.

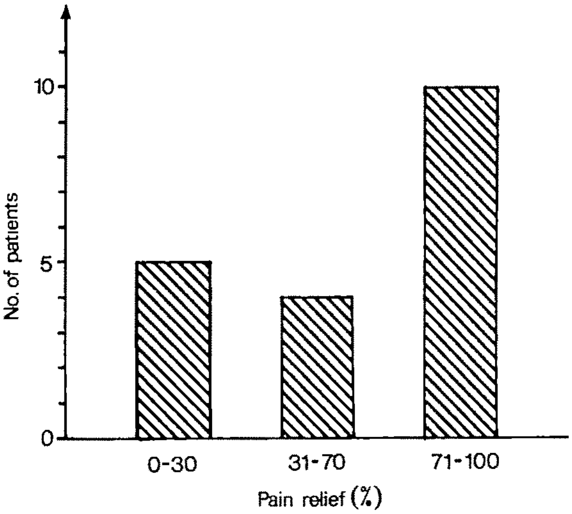

FIG. 1. Analgesic effect after 20 min expressed as per cent pain relief derived from the visual analogue scale. The patients are grouped in three categories, corresponding to the subjective judgements of pain relief.

Table I shows how pethidine in the extradural space influences temperature and pin-prick discrimination and the sensation of heavy legs. In the group with good or excellent analgesia eight of 14 patients had a segmental involvement of at least one of these three variables. In two of the five patients

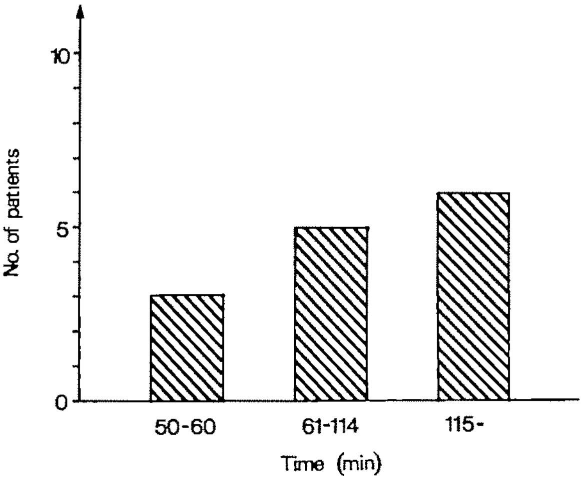

FIG. 2. Duration of analgesia of the 14 patients with good or excellent pain relief. The time limits in the three groups are arbitrarily chosen. In the group with a duration of more than 115 min the accurate duration could not be decided because in three patients the duration of analgesia outlasted the delivery.

TABLE I. *Number of patients with segmental effects of extradural pethidine. The two patients with impaired pin-prick discrimination in the group with poor analgesia had this effect in T3–9 and T9–11 respectively. In the group with good or excellent analgesia the four patients with effect on temperature discrimination and the six patients with heavy legs all had effect on pin-prick discrimination*

	Number of patients with	
Segmental effect on	poor analgesia ($n = 5$)	good or excellent analgesia ($n = 14$)
Pin-prick	2	8
Temperature	0	4
Heavy legs	0	6

TABLE II. *Pethidine concentration (ng ml^{-1}) in plasma for patients given an extradural dose of pethidine 25 mg with or without adrenaline. Only concentrations before bupivacaine with adrenaline were administered are included*

	Pethidine plasma concn (ng ml^{-1}) after (min)				
Patient	5	15	30	60	90
With adrenaline					
1	24	65	55	—	—
2	0	45	45	—	—
3	33	53	34	34	38
4	9	58	48	47	43
5	44	71	61	57	50
6	12	43	36	45	41
7	72	51	33	—	—
8	82	95	88	69	63
9	16	40	48	47	52
Median values	24	53	48	47	46.5
Without adrenaline					
1	14	88	91	110	—
2	5	53	53	—	—
3	55	71	107	99	84
4	30	118	69	46	—
5	36	57	74	51	—
6	61	73	141	—	—
7	93	188	134	91	—
8	16	40	48	47	52
Median values	33	72	71.5	71	—

with poor analgesia impaired pin-prick discrimination was found in T3–9 and T9–11 respectively. No patient in this group had any involvement of the entire segment T10–L1 whereas all of the patients in the group with good or excellent analgesia had a segmental distribution that included T10–L1 or more.

Respiratory depression was not observed in any of the women. Two infants had an Apgar score less than 7 at 1 min, and one was still less than 7 at 5 min. In both of these infants instrument-assisted delivery was necessary because of threatening asphyxia.

The plasma concentrations of pethidine varied widely in both groups (table II) and the median value was less for the group who had received pethidine with adrenaline. Figure 3 shows a representative plasma concentration curve for one patient and demonstrates that the concentration of pethidine was comparatively stable for several hours. No relationship between plasma concentrations of pethidine and analgesic effect after 20 min was found.

The plasma concentrations of pethidine in mixed umbilical blood ranged from 10 to 96 ng ml^{-1} with a median value of 32 ng ml^{-1}. They were slightly less than the maternal plasma concentration at birth (fig. 3).

In one of the patients nausea occurred 30 min after the administration of pethidine. In no patient did hypotension or itching occur.

DISCUSSION

A single extradural dose of pethidine 25 mg provided good or excellent analgesia in labour in 14 of the 19 women studied. The duration of pethidine-induced analgesia was evaluated only indirectly, taking the time of required additional analgesia as end-point. Thus it was estimated that the duration lasted for 50–160 min, which constituted 13–100% of the total delivery time (fig. 4). The small difference in the median values for pain relief between the two groups cannot serve as a basis for any conclusions since, in the group of 10 patients with adrenaline, three were nulliparous and in the group of nine without adrenaline six were nulliparous.

To obtain effective analgesia during the first stage of labour T10–L1 should be blocked (Bonica, 1979). We found signs of segmental analgesia with reduced temperature and pin-prick discrimination or sensation of heavy legs, or both, in 57% of the patients with effective pethidine analgesia. This contrasts with reports from others (Husemeyer, O'Connor and Davenport, 1980; Perriss, 1980). Bromage, Camporesi and Leslie (1980) reported a dose-dependent regional decrease of discrimination for pin-prick and temperature after extradural doses of methadone, hydromorphone or morphine.

The peak plasma concentrations of pethidine after extradural administration were small (45–188 ng ml^{-1}) compared with the concentrations (300–650 ng ml^{-1}) found in parturients after i.m.

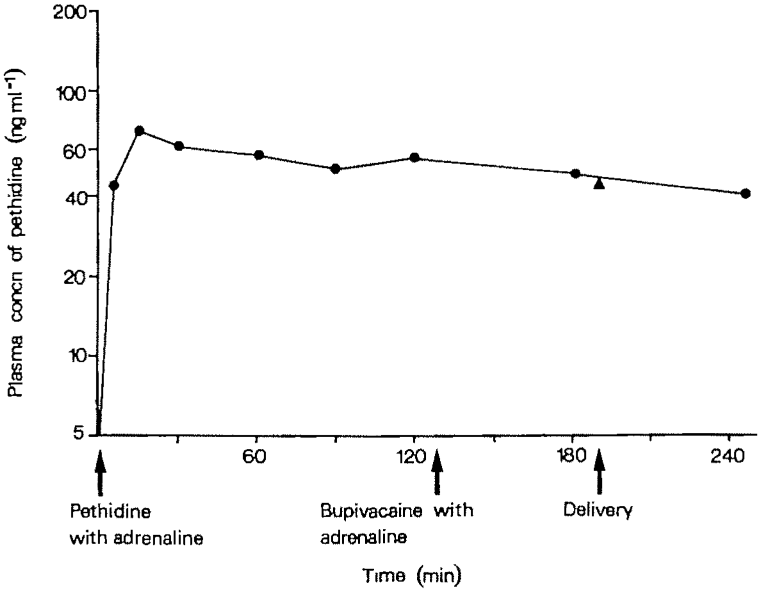

FIG. 3. Plasma concentrations of pethidine (ng ml^{-1}) in one patient after extradural pethidine 25 mg with adrenaline. ● = Maternal plasma concentration; ▲ = umbilical plasma concentration.

injection of 1.5 mg/kg body weight (G. Tomson and colleagues, in preparation). However, the peak plasma concentrations were greater after extradural administration than would be expected after a similar dose administered i.m. (Tomson and colleagues, in preparation). These characteristics of extradural pethidine, with the sustained plasma concentrations observed (fig. 3) may lead to respiratory depression after repeated administration of even low doses.

Since segmental effects were observed and good or excellent analgesia was achieved, even though the plasma concentrations of pethidine were low, a direct spinal action is indicated.

We found that almost 75% of the women experienced good or excellent analgesia. This is in contrast to the inadequate or absent pain relief after administration of extradural morphine during labour (Husemeyer, O'Connor and Davenport, 1980; Magora et al., 1980; Nybell-Lindahl et al., 1981; Writer, James and Wheeler, 1981). As morphine is not as lipophilic as pethidine it probably takes longer for morphine to reach the spinal cord (Yaksh, 1981). One study reports acceptable analgesia from morphine 2.5–4.0 mg given extradurally in labour in 12 of 25 patients (Booker et al., 1980), but the reported latency periods vary between 15 and 40 min. This long latency period can be the reason why others have failed to achieve analgesia with extradural morphine during labour.

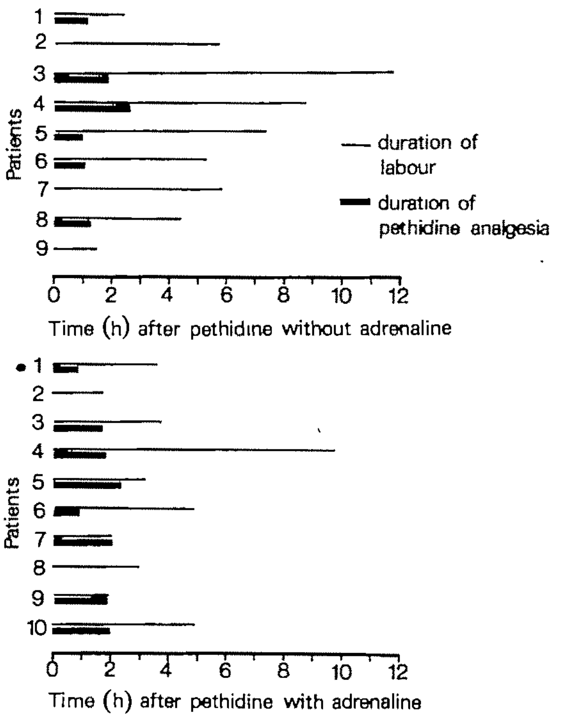

FIG. 4. Graphic presentation of duration of good or excellent analgesia from pethidine, with or without adrenaline, in relation to time until delivery.

The frequency of adequate analgesia with pethidine in the extradural space is less than with local anaesthetics. With extradural bupivacaine the expected frequency of adequate analgesia is about 95% (Moir, 1976). The risk of respiratory depression in the mother or the infant following repeated doses of extradural pethidine argues against the routine use of this technique. In conclusion extradural pethidine, with or without adrenaline, does not seem to provide a safe alternative to local anaesthetics in labour.

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LA PETHIDINE AVEC OU SANS ADRENALINE EN PERIDURALE AU COURS DU TRAVAIL: EFFETS EXTREMEMENT VARIABLES

RESUME

On a étudié l'effet analgésique d'une dose péridurale unique de pethidine 25 mg avec ou sans adrénaline chez 20 femmes bien portantes au cours du travail. L'étude était découverte pour ce qui est des effets de la péthidine, mais en double aveugle pour ce qui est de l'adjonction d'adrénaline. Chez 14 femmes sur 19, une analgésie bonne ou excellente a été obtenue pendant une période 50–160 min. La pethidine additionnée d'adrénaline 25 µg n'était pas plus efficace que la péthidine seule. Huit de ces 14 femmes avaient des signes d'anesthésie régionale à la piqûre d'épingle et pour la discrimination thermique. La concentration plasmatique de péthidine était faible (45–188 mg ml^{-1}). Chez huit patientes, on a pû retrouver de la péthidine dans le plasma pendant plus de 90 min. Ainsi, la péthidine en péridurale entraîne une analgésie de durée variable et faible. Des doses répétées peuvent être nécessaires, et entraîner une accumulation plasmatique de l'agent, avec un risque de dépression respiratoire chez la mére ou l'enfant.

EPIDURALE PETHIDIN-GABE MIT UND OHNE ADRENALINE WÄHREND DER GEBURT: GROßE STREUUNG DER WIRKUNG

ZUSAMMENFASSUNG

Die schmerzlindernde Wirkung einer einzigen epiduralen Dosis von 25 mg Pathidin mit und ohne Adrenaline wurde bei 20 gesunden Frauen während der Geburt untersucht. Die Untersuchung war offen, was die Wirkung von Pethidin betrifft, aber doppel blind im Hinblick auf den Adrenalin-Zusatz. Vierzehn von 19 Frauen gaben für eine Zeit von 50 bis 160 Minuten eine ausgezeichnete Schmerzfreiheit an. Pethidin mit 25 mg Adrenalin war nicht wirksamer als Pethidin allein. Acht von 14 Frauen zeigten Zeichen einer Regionalanästhesie, was mittels "Nadelpieken" und Temperaturempfindungen festgestellt wurde. Die Patientinnen hatten niedrige Pethidin-Konzentrationen im Plasma (45–188 ng ml^{-1}). Bei 8 Patientinnen war die Pethidin-Plasmakonzentration für mindestens eine halbe Stunde nachweisbar. Epidural appliziertes Pethidin verursacht eine Analgesie

von kurzer und wechselnder Dauer. Wiederholte Gaben sind unter Umständen erforderlich, diese können aber zu einer Akkumulation des Mittels im Plasma führen mit der Gefahr der Atemdepression bei Mutter und Kind.

PETIDINA EXTRADURAL CON Y SIN ADRENALINA DURANTE EL PARTO: GRAN VARIACION EN LOS EFECTOS

SUMARIO

Se llevó a cabo un estudio del efecto aliviador del dolor de una dosis única extradural de 25 mg de petidina con y sin adrenalina en 20 mujeres sanas durante el parto. El estudio era abierto en lo que se refiere a los efectos de la petidina, pero doble-ciego en cuanto a la añadidura de adrenalina. En 14 de las 19 mujeres, se obtuvo una analgesia excelente por un periodo de 50–160 min. La petidina con 25 μg de adrenalina no fue más eficaz que la petidina sola. Ocho de las 14 mujeres demostraron señales de analgesia regional con picadura de alfiler y una discriminación de temperatura. Las pacientes tenían pequeñas concentraciones (45-188 ng ml^{-1}) de petidina en el plasma. En ocho de las pacientes, las concentraciones de petidina en el plasma se mantuvieron por lo menos durante 1.5 h. La petidina extradural entonces induce la analgesia de duración corta y variable. Dosis repetidas pueden ser necesarias, lo que resulta en una acumulación de la substancia en el plasma con riesgos de depresión respiratoria en la madre o en el niño.

Br. J. Anaesth. (1982). 54, 421

PAIN RELIEF AFTER ABDOMINAL SURGERY—A COMPARISON OF I.M. MORPHINE, SUBLINGUAL BUPRENORPHINE AND SELF-ADMINISTERED I.V. PETHIDINE

R. ELLIS, D. HAINES, R. SHAH, B. R. COTTON AND G. SMITH

SUMMARY

One hundred and twenty-six patients undergoing upper and lower abdominal surgery were studied after operation to compare the analgesic effects of i.m. morphine, sublingual buprenorphine and self-administered i.v. pethidine by Cardiff Palliator. There were no significant differences between analgesic regimens in respect of subjective linear analogue pain scores or static and dynamic lung volumes assessed at 24 and 48 h after operation and 5 days after operation in patients who underwent upper abdominal surgery. Sublingual buprenorphine produced more nausea and sedation than the other two treatments, but the differences were not clinically important. However, it offered considerable advantages in terms of ease of administration.

I.m. analgesic drugs given continually on demand are generally regarded as providing inadequate control of pain for patients in the period after operation (Keeri-Szanto and Heaman, 1972), probably because of the intermittent nature of drug administration, in addition to variability in rates of absorption, and perhaps a failure of medical and nursing staff to recognize the patient's need for analgesia.

Two recently described analgesic regimens may obviate these problems. Chakravarty and his colleagues (1979) described the safe and effective use of a patient-controlled i.v. analgesic apparatus (the Cardiff Palliator) to relieve pain following upper abdominal surgery, but did not compare its performance with an i.m. regimen. Nonetheless, this apparatus has since been marketed commercially, calibrated for use with pethidine and with instructions describing the clinical use of the equipment. However, it seemed to us that there is a need for a "field trial" of this equipment despite the obvious difficulties of undertaking a comparison of self-administered analgesic with intermittent i.m. administration.

Buprenorphine, a potent synthetic analgesic, achieves higher opiate receptor occupancy of long duration. The slow dissociation constant of the drug–receptor complex permits a prolonged drug effect in the presence of low plasma concentrations (Bullingham et al., 1980). Fry (1979) has shown that buprenorphine administered sublingually on demand provided good analgesia in patients following lower abdominal surgery. A regular sublingual dosage regimen of buprenorphine would appear to take maximum advantage of the long duration of action, its ease of administration, and its low potential to produce respiratory depression. Such a regimen has not been described previously in the treatment of pain after operation.

This study was therefore designed to answer two questions as economically as possible: first, does the Cardiff Palliator provide superior analgesia to conventional i.m. analgesia when used for the *same duration* in a routine postoperative surgical ward in which there has been minimal alteration in ward nursing routine? (This is the first "field trial" of this equipment.) Second, does sublingual buprenorphine provide analgesia comparable to that obtained by conventional analgesia?

METHODS

Patients included in these studies were all selected from a single complex containing both gynaecological and general surgical patients under the care of either two consultant gynaecologists or two consultant surgeons. The studies were confined to three standard surgical procedures: cholecystectomy, hysterectomy or herniorrhaphy. All patients were in the age range 18–65 yr, and only those devoid of significant respiratory or cardiovascular dysfunction and within 10% of expected body weight were included in the study. No patient was receiving analgesic or sedative drugs routinely at the time of hospital admission. After giving informed con-

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sent, patients undergoing cholecystectomy were allocated randomly to one of the three analgesic regimens under study. In order to obtain the maximum number of patients for comparison purposes, patients undergoing herniorrhaphy were allocated to only one of two groups, conventional i.m. morphine and buprenorphine for postoperative analgesia. Similarly, patients undergoing hysterectomy were allocated to receive either conventional i.m. morphine or self-administered pethidine by Cardiff Palliator. Because only one Palliator was available for use in these studies, hysterectomy patients were randomly chosen according to non-utilization of the Palliator for cholecystectomy patients. This yielded a total of only 20 hysterectomy patients in a 15-month period, and these patients were then matched against 20 patients obtained by computer from a bank of hysterectomy patients under investigation for other studies, matching age, weight and height. It is unlikely that this process would be likely to induce bias either towards conventional analgesia or towards self-administered analgesia, as all patients had agreed to enter this investigation with a 20–30% chance of being offered the Palliator for pain relief after operation.

Each patient received diazepam 10–20 mg orally 1 h before surgery, and anaesthesia was induced with thiopentone and maintained by nitrous oxide in oxygen and neuromuscular blockade, supplemented by morphine, buprenorphine or pethidine according to the mode of postoperative analgesia. After operation patients received one of the three analgesic treatments under study: (1) buprenorphine 0.4 mg sublingually 6-hourly; (2) morphine 10 mg i.m. on demand according to the usual practice of the ward nursing staff; (3) pethidine i.v. by the patient-controlled apparatus (the Cardiff Palliator).

Pulmonary function testing was carried out on all patients before operation and on the 1st and 2nd days after operation and also on the 5th day in those patients undergoing cholecystectomy. Measurements were made using the Gould Godart pulmonary function laboratory and included functional residual capacity (FRC), forced expiratory volume in 1 s ($FEV_{1.0}$) and peak expiratory flow rate (PEFR). All patients received the instruction and practice in performance of the tests which were always carried out with the subject in a sitting position using a well-fitting mouthpiece and noseclip.

In the period after operation linear analogue pain scores were recorded by each patient at the time of pulmonary function testing. Linear analogue scores for sedation and nausea were obtained also.

Measurements were made in the postoperative period at approximately 24 and 48 h after operation, and also at 5 days after operation in the cholecystectomy group. Because of the considerable variation in the duration of action of the three different modes of administration of analgesic, it was not possible to specify these assessments at a specific time in relationship to the administration of analgesia, but it was ascertained at the time of testing that the patient was not more uncomfortable subjectively than he or she felt in the preceding 2–4 h.

Those patients who had been allocated to receive the patient-controlled i.v. analgesia apparatus were instructed in its use during the preoperative interview.

Thus, three groups of patients were studied: group A = 48 patients undergoing cholecystectomy allocated randomly to receive one of the three analgesic regimens; group B = 38 patients undergoing inguinal herniorrhaphy allocated randomly to receive either buprenorphine or morphine; group

TABLE I. *Patient data in the three groups (mean ± SEM)*

	Group A (Cholecystectomy)					Group B (Herniorrhaphy)					Group C (Hysterectomy)				
Drug	No.	Age (yr)	Ht. (cm)	Wt. (kg)	Duration of op. (min)	No.	Age (yr)	Ht. (cm)	Wt. (kg)	Duration of op. (min)	No.	Age (yr)	Ht. (cm)	Wt. (kg)	Duration of op. (min)
Buprenorphine	16 (5M)	51.3 ±4.3	163.5 ±2.1	64.3 ±3.6	93.1 ±5.5	19 (17M)	51.7 ±2.7	171.4 ±1.6	72.0 ±2.1	61.3 ±3.9					
Morphine	17 (5M)	53.7 ±3.5	165.1 ±1.9	66.9 ±2.1	101.5 6.7	19 (18M)	54.7 2.5	172.3 ±1.9	75.5 ±2.3	62.9 ±5.5	20	47.2 ±2.3	161.9 ±1.2	62.9 ±1.8	61.4 ±6.4
Pethidine	15 (3M)	50.8 ±4.6	165.5 ±2.6	66.2 ±1.7	91.8 ±5.5						20	44.3 ±1.7	160.8 ±1.3	64.0 ±1.7	62.2 ±4.0

TABLE II. *Linear analogue pain scores (0 = no pain, 10 = maximum) (mean ± SEM)*

	Group A			Group B		Group C	
	Day 1	Day 2	Day 5	Day 1	Day 2	Day 1	Day 2
Buprenorphine	3.3	3.0	1.0	1.8	1.7		
	±0.5	±0.6	±0.3	±0.4	±0.4		
Morphine	3.9	2.2	1.5	2.5	1.9	3.5	2.3
	±0.6	±0.6	±0.4	±0.5	±0.4	±0.7	±0.4
Pethidine	4.3	2.6	1.3			2.7	2.9
	±0.8	±0.5	±0.5			±0.5	±0.6

C = 20 patients undergoing total abdominal hysterectomy allocated to receive pethidine by Cardiff Palliator and compared with 20 patients matched for height and weight who had received conventional morphine analgesia for pain after operation.

After 48 h in both the hysterectomy and herniorrhaphy patients, an attempt to obtain an assessment of the overall quality of postoperative analgesia was obtained by asking the patient to complete a simple questionnaire. This comprised three questions: (1) "How satisfied were you with your analgesia?" Answer: Totally dissatisfied; moderately dissatisfied; moderately satisfied; totally satisfied. (2) "Would you be happy to have the same type of analgesia for any future operation?" Answer: Yes or No. (3) "Did you feel more pain than you expected?" Answer: Yes or No.

Linear analogue scores were anlysed using the Wilcoxon rank sum test. Other data were compared statistically using either Student's t test or χ^2 tests as appropriate. $P < 0.05$ was taken as an indication of statistical significance.

RESULTS

Analysis of the data revealed no significant differences within groups in respect of age, sex, height or weight (table I). There were no significant differences between treatments within each of the three groups in respect of linear analogue pain scores (table II), or pulmonary function measurements (tables III–V).

In group A patients undergoing cholecystectomy, mean linear pain scores were in the range 3.3–4.3 on day 1, and in the range 2–3 on day 2. Changes in FEV$_{1.0}$ exhibited the greatest decrease on the 1st day after operation to approximately 50% of the value before operation. This increased to 60% on day 2, and to 75% of the postoperative values by the 5th day after operation (table III). The pattern of changes in FRC was similar, but of lesser magnitude. The greatest decrease occurred on day 1 to 75% of the preoperative value, increasing to 80% on day 2, and to 90% by day 5 (table IV). Similar changes occurred in peak expiratory flow rate (table V).

In group A, the linear analogue scores for sedation were significantly greater for buprenorphine in comparison with morphine on day 2 ($P < 0.025$) and also with both morphine ($P < 0.05$) and pethidine ($P < 0.01$) on day 5 (table VI). In the buprenorphine group the score for nausea on day 1 was greater than that in the pethidine group ($P < 0.01$) (table VII). In group B patients undergoing herniorrhaphy, pain scores were significantly lower than in the cholecystectomy group on day 1, and there was less impairment of pulmonary function (tables III–V). The

TABLE III. *FEV$_{1.0}$ values (litre) in patients before and after operation (mean ± SEM)*

	Group A				Group B			Group C		
	Pre-op	Day 1	Day 2	Day 5	Pre-op	Day 1	Day 2	Pre-op	Day 1	Day 2
Buprenorphine	2.07	1.03	1.32	1.60	2.99	2.38	2.70			
	±0.17	±0.11	±0.14	±0.16	±0.16	±0.19	±0.17			
Morphine	2.25	1.13	1.38	1.60	3.11	2.59	2.73	2.12	1.43	1.60
	±0.26	±0.11	±0.16	±0.19	±0.23	±0.23	±0.22	±0.13	±0.11	±0.12
Pethidine	2.50	0.98	1.26	1.95				2.34	1.63	1.77
	±0.21	±0.08	±0.10	±0.16				±0.09	±0.09	±0.11

TABLE IV. *Functional residual capacity (litre) in patients before and after operation (mean ± SEM)*

	Group A				Group B			Group C		
	Pre-op	Day 1	Day 2	Day 5	Pre-op	Day 1	Day 2	Pre-op	Day 1	Day 2
Buprenorphine	2.27 ±0.16	1.66 ±0.13	1.85 ±0.13	2.01 ±0.19	2.64 ±0.16	2.29 ±0.15	2.48 ±0.17			
Morphine	2.50 ±0.19	1.79 ±0.16	2.02 ±0.16	2.25 ±0.19	2.76 ±0.16	2.61 ±0.16	2.78 ±0.18	2.58 ±0.14	2.09 ±0.15	2.31 ±0.16
Pethidine	2.47 ±0.18	2.04 ±0.22	2.05 ±0.17	2.43 ±0.16				2.50 ±0.11	1.98 ±0.09	2.24 ±0.12

TABLE V. *Peak expiratory flow rates (litre s^{-1}) in patients before and after operation (mean ± SEM)*

	Group A				Group B			Group C		
	Pre-op	Day 1	Day 2	Day 5	Pre-op	Day 1	Day 2	Pre-op	Day 1	Day 2
Buprenorphine	4.31 ±0.57	2.00 ±0.26	2.30 ±0.24	3.09 ±0.33	5.92 ±0.66	5.13 ±0.55	5.58 ±0.47			
Morphine	4.47 ±0.55	2.29 ±0.31	2.54 ±0.32	2.94 ±0.36	6.31 ±0.60	5.10 ±0.50	5.55 ±0.45	3.49 ±0.23	2.27 ±0.15	2.45 ±0.17
Pethidine	4.42 ±0.47	1.93 ±0.12	2.21 ±0.21	3.51 ±0.35				3.89 ±0.26	2.78 ±0.25	2.97 ±0.28

TABLE VI. *Linear analogue sedation scores (0 = no sedation, 10 = maximum) (mean ± SEM).* *$P < 0.05$

	Group A			Group B		Group C	
	Day 1	Day 2	Day 5	Day 1	Day 2	Day 1	Day 2
Morphine	6.1 ±0.7	3.4 ±0.7 *	1.4 0.6 *	3.1 ±0.7	2.8 ±0.6	6.0 ±0.7	3.2 ±0.6
Buprenorphine	6.8 ±0.7	5.8 ±0.8	3.0 ±0.8 *	4.3 ±0.8	2.6 ±0.6		
Pethidine •	4.8 ±0.8	3.7 ±1.0	0.4 0.2			5.8 ±0.7	2.4 ±0.7

TABLE VII. *Linear analogue nausea scores (0 = no nausea, 10 = maximum) (mean ± SEM).* *$P < 0.05$

	Group A			Group B		Group C	
	Day 1	Day 2	Day 5	Day 1	Day 2	Day 1	Day 2
Morphine	1.8 ±0.6	1.2 ±0.5	0.3 ±0.1	1.2 ±0.4	1.0 ±0.4	3.4 ±0.7	1.1 ±0.4
Buprenorphine	3.0 ±0.8 *	1.4 ±0.5	0.4 ±0.2	2.1 ±0.7	1.3 ±0.6		
Pethidine	0.4 ±0.1 •	2.3 ±0.8	0.4 ±0.2			2.3 ±0.7	2.0 ±0.7

TABLE VIII. *Doses of opiates (mg) (mean SEM). Day 1 values represent total dosage in first 24 h after operation excluding doses administered during operation. Day 2 represents the dose administered from 24 to 48 h*

	Group A			Group B			Group C		
	Intra-op	Day 1	Day 2	Intra-op	Day 1	Day 2	Intra-op	Day 1	Day 2
Buprenorphine	0.9 ±0.4	1.6 ±0.1	1.5 ±0.1	0.5 ±0.03	1.4 ±0.1	1.3 ±0.1			
Morphine	12.0 ±0.9	38.4 ±2.5	29.4 ±1.9	8.8 ±0.5	16.5 ±1.9	9.2 ±0.8	13.7 ±5.2	39.8 ±2.3	17.9 ±2.6
Pethidine	90.7 ±10.1	376.6 ±46.6	272.8 ±55.4				80.0 ±10.9	424.3 ±44.0	167.3 ±20.5

frequencies of side-effects for morphine and buprenorphine (tables VI–VII) were not significantly different.

In group C pain scores were intermediate between those of groups A and B, as was the impairment of pulmonary function. There were no differences between morphine and self-administered pethidine in the frequency of side-effects.

Pulmonary function measurements expressed as a percentage of their respective values before operation exhibited a significant negative correlation with linear analogue pain scores. For all patients on day 1, the correlation was better for both PEFR ($r = -0.245$, $P < 0.01$) and $FEV_{1.0}$ ($r = -0.211$, $P < 0.05$) than for FRC ($r = -0.184$, $P < 0.05$).

There was no significant difference between the frequency of postoperative chest infection, as diagnosed by the primary medical attendants, occurring in the cholecystectomy group of patients for any of the three groups (buprenorphine, three patients; pethidine, one; morphine, two). Additionally, there were no significant differences in the response to the patient questionnaire between the analgesic regimens for each operation (table IX).

DISCUSSION

This study demonstrates that regular sublingual buprenorphine, well conducted conventional i.m. morphine and i.v. pethidine infusion from a patient-controlled apparatus, afforded a similar degree of analgesia.

Management of the extent of pain relief induced by drugs is notoriously difficult and a rigid comparison between drugs requires a double-blind compari-

TABLE IX. *Patient questionnaire completed at 2 days for hysterectomy and herniorrhaphy and at 5 days for cholecystectomy*

	Satisfaction				Same analgesia again		More pain than expected	
	Total dissatisfaction	Moderate dissatisfaction	Moderate	Total	Yes	No	Yes	No
Cholecystectomy								
Palliator ($n = 15$)	0	0	3 (20%)	12 (80%)	15 (100%)	0	5 (33%)	10 (67%)
Morphine ($n = 17$)	0	0	4 (23.5%)	13 (76.5%)	17 (100%)	0	7 (41%)	10 (59%)
Buprenorphine ($n = 16$)	0	0	1 (6.2%)	15 (93.8%)	16 (100%)	0	3 (19%)	13 (81%)
Hernia								
Morphine ($n = 19$)	0	1 (5.3%)	6 (31.6%)	12 (63.1%)	18 (94.7%)	1 (5.3%)	3 (15.8%)	16 (84.2%)
Buprenorphine ($n = 19$)	1 (5.3%)	0	6 (31.6%)	12 (63.1%)	18 (94.7%)	1 (5.3%)	2 (10.5%)	17 (89.5%)
Hysterectomy								
Morphine ($n = 20$)	0	0	11 (55%)	9 (48%)	19 (95%)	1 (5%)	4 (20%)	16 (80%)
Palliator ($n = 20$)	0	2 (10%)	8 (40%)	10 (50%)	16 (80%)	4 (20%)	6 (33%)	12 (66%)

son when subjective modes of assessing analgesia are used. However, this invariably affects medical and nursing activities and alteration in postoperative routine management may modify analgesia. In this study alteration in ward activity was kept to the minimum and although subjective linear analogue scores were used, we have compared the results with a more objective assessment in the form of respiratory function tests. However, the subjective visual analogue score was found to be both accurate and repeatable in obstetric patients (Revill et al., 1976) and has been generally accepted as a reasonable test for severe pain (Rosen, 1977).

The scores obtained here are similar to those reported elsewhere in patients receiving self-administered pethidine and buprenorphine after upper abdominal surgery (Chakravarty et al., 1979). $FEV_{1.0}$ is known to be a more sensitive parameter of respiratory function than FRC in response to pain (Rosen, 1977) and $FEV_{1.0}$ as a percentage of preoperative values has been acknowledged as the most sensitive respiratory parameter (Bromage, Camporesi and Chestnut, 1980). In this study, we found that visual analogue scores exhibited the best correlation with PEFR and confirmed that the correlation with $FEV_{1.0}$ was slightly better than that for FRC (expressed as % of values before operation).

When comparing analgesic drugs it is important to apply assessment at similar periods with respect to analgesic plasma concentrations. When drugs have comparable duration of action, this is achieved easily by obtaining measurements at fixed times following administration, but this was not possible in the present study. In addition, it was not possible to specify a time of assessment exactly 24 h after operation, as this may bear no relationship to comparable periods of analgesia. The device we adopted, therefore, was to approach the patient at approximately 24 h after operation and the patient was asked if he felt at that moment as comfortable as within the previous 2–4 h. If the answer was in the affirmative, assessment was undertaken. We hoped that, by utilizing this timing of assessment, there would be a random distribution of time of assessment with respect to time of the immediately prior injection for administration of analgesic. In every instance the answer was in the affirmative, which should indeed have produced random scatter of timings. In addition, if this aspect of our assessment were likely to introduce any bias, it would seem most probable that the bias would be pro-Palliator and against intermittent i.m. injections. Nonetheless, it should be recognized that this is only an assessment of a brief period of time during the whole of the postoperative period. The measurement of $FEV_{1.0}/FVC$ represents an index of the amount of pain experienced at the exact moment of testing, whilst there is an indication that FRC changes may be representative of the *overall* quality of pain relief. This is suggested by the finding of Spence and Logan (1975) that, after cholecystectomy, FRC changes were less impaired with 4-hourly morphine than with less frequently administered morphine on demand. However, the differences were small as FRC changes are possibly affected only to a small extent by pain and to a large extent by such conditions as pneumoperitoneum. Therefore, in an attempt to supplement the assessment of the overall 48 h "package" of postoperative analgesia, we applied a simple patient questionnaire at the end of the study (2 days for hernia and hysterectomy, 5 days for cholecystectomy). The accuracy of linear analogue pain scores has been demonstrated only in terms of pain appreciated around the time of its application, therefore it did not seem acceptable to ask patients to score *maximum* and *minimum* pain at the time of testing.

It is important to note that patients in our study given conventional "on demand" i.m. analgesics by the nursing staff received larger doses of morphine than may be administered in other surgical units. This is reflected by the finding that the total dose of morphine given to patients following vagotomy and pyloroplasty in the study by Alexander, Parikh and Spence (1973) was 46.7 mg (mean) in comparison with a 48 h dosage of 67.8 mg (table VIII) following cholecystectomy in our study. The amount of systemic analgesia given is known to have a bearing on postoperative respiratory function. Thus, Alexander, Parikh and Spence (1973) found that morphine 10 mg 4-hourly produced marginal improvement in vital capacity in comparison with morphine "on demand".

The amount of pethidine self-administered by the patients in our study was similar to that self-administered by patients in the study by Chakravarty and colleagues (1979). In the latter study, 595 mg of pethidine (mean for 15 patients) was given in patients undergoing upper abdominal surgery in comparison with 649 mg in this study (table IX). Thus, it would appear that the self-administration system, when utilized in a "normal manner", does not provide analgesia superior to that obtained by either sublingual buprenorphine or well administered conventional i.m. morphine analgesia. However, there may be greater fluctuations in plasma pethidine concentrations than anticipated.

Since Stapleton, Austin and Mather (1979) demonstrated that, on cessation of a continuous i.v. infusion of pethidine, the plasma concentration may decrease to a subanalgesic value in as short a period as 2.5 h, in the 48 h period of this study, a decrease to subanalgesic concentrations may have occurred, for example during sleep. This problem might be obviated by a more sophisticated apparatus, such as that described by White, Pearce and Norman (1979), which provides a background continuous infusion in addition to a patient-operated supplement.

The frequency of side-effects with buprenorphine reported in previous studies has varied. Hovell (1977) observed more sedation with buprenorphine in comparison with pethidine, whilst Kay (1978) reported a similar trend when compared with morphine. Downing, Leary and White (1977) found no difference in side-effects on comparing buprenorphine with morphine. In our study, linear analogue scoring of side-effects revealed greater sedation and nausea with buprenorphine only in the patients undergoing cholecystectomy. However, the difference in scores was small, and although statistically significant, did not appear to represent a clinical problem. Differences in levels of sedation may be the result partly of the regular dosage schedule of buprenorphine throughout the 48-h period when administration of the other two analgesics was becoming less frequent (table VIII). The increased degree of nausea experienced in the buprenorphine group may also be explained partly by the lower dosage of prochlorperazine administered. In our hospital it is standard nursing practice for prochlorperazine to be administered routinely with parenteral doses of morphine, but this routine was not followed with unfamiliar modes of analgesia.

The object of this study was to see if, in a routine postoperative surgical ward with minimal interference with nursing activities, the use of the Cardiff Palliator would be associated with better postoperative analgesia than that accompanying conventional i.m. analgesia, and in addition, if the use of buprenorphine with its long receptor occupancy produced improved analgesia. However, it appears from our results that there was little difference in the degree of analgesia achieved by the three techniques. It is concluded that the Cardiff Palliator is unlikely to achieve a role in the routine management of postoperative pain on the grounds of expense (cost > £1000), failure to achieve superior analgesia (with pethidine), and the necessity to maintain a patent i.v. infusion cannula. This statement requires qualification to the extent that in the present study we used pethidine because the apparatus is supplied by the manufacturer calibrated for use with this drug. Assessment of the extent of analgesia achieved using the same drug by both apparatus and conventional administration would be required before denying any possible advantages existed with apparatus administration. In contrast, however, buprenorphine achieved analgesia comparable to the other two regimens and also exhibited several important administrative advantages. It was dispensed on the regular ward drug round (6-hourly), is not governed by Controlled Drug Regulations, and the route of administration is non-parenteral.

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ANALGESIE APRES CHIRURGIE ABDOMINALE. UNE COMPARAISON ENTRE LA MORPHINE I.M., LA BUPERENORPHINE SUBLINGUALE ET LA PETHIDINE I.V. AUTO-ADMINISTREE

RESUME

Nous avons étudié, aprés l'intervention, 26 patients subissant des actes de chirurgie abdominal sus et sous mesocolique pour comparer les effets analgésiques de la morphine i.m., de la buprenorphine sublinguale et de la péthidine i.v. auto-administrée par le Cardiff Palliator. Il n'y a pas eu de différences significatives entre les protocoles d'analgésie pour ce qui concerne l'intensité subjective linéaire comparée de la douleur ou les spirométries statiques et dynamiques mesurées à la 24ᵉ et à la 48ᵉ heure postopératoires, puis 5 jours après l'intervention pour ce qui concerne les patients opérés de l'étage sus-mésocolique. La buprénorphine sublinguale a été responsable de plus de nausées et de somnolence que les deux autres traitements, mais les différences restaient peu importantes en clinique. Cependant, cette voie d'administration offrait des avantages considérables de facilité d'emploi.

SCHMERZBEKÄMPFUNG NACH BAUCHCHIRURGISCHEN EINGRIFFEN. VERGLEICH DER WIRKUNG VON MORPHIN I.M., BUPRENORPHIN SUBLINGUAL UND VOM PATIENTEN SELBST VERABREICHTES PETHIDIN I.V.

ZUSAMMENFASSUNG

Bei 126 Patienten, die sich chirurgischen Eingriffen am Ober- und Unterbauch zu unterziehen hatten, wurde die Wirkung von Morphin i.m., Buprenorphin sublingual und von Pethidin i.v., das sich der Patient selbst mit dem "Cardiff Palliator" in der postoperativen Phase verabreicht, verglichen. Es gab keine signifikanten Unterschiede zwischen der Analgetika-Verabreichung im Hinblick auf die subjektiv angegebenen Schmerz-scores, auf das statistisch erfaßte und dynamisch gemessene Atemvolumen nach 1, 2 und 5 Tagen bei Patienten mit Oberbaucheingriffen. Buprenorphin sublingual rief häufiger Übelkeit und stärkere Sedierung hervor als die beiden anderen Behandlungen, was klinisch ohne Bedeutung war. Von Vorteil ist jedoch seine angenehme Verabreichungsart.

ALIVIO DEL DOLOR DESPUES DE LA INTERVENCION ABDOMINAL: UNA COMPARACION DE LA MORFINA INTRAMUSCULAR, DE LA BUPRENORFINA SUBLINGUAL Y DE LA PETIDINA INTRAVENOSA AUTOADMINISTRADA

SUMARIO

Se estudiaron ciento veintiseis pacientes después de someterles a intervención quirúrjica de la parte superior e inferior del abdomen, con el fin de comparar los efectos analgésicos de la morfina intramuscular, de la burprenorfina sublingual y de la petidina intravenosa autoadministrada mediante el Cardiff Palliator. No se presentaron diferencias significativas entre los diversos regímenes analgésicos, en lo tocante a las puntuaciones de dolor de la analogía lineal subjetiva ni de los volúmenes estáticos o dinámicos evaluados después de transcurridas 24 h y 48 h de la intervención, así como después de 5 días de ésta, en los pacientes sometidos a intervención quirúrjica de la parte superior del abdomen. La buprenorfina sublingual produjo más náusea y sedación que los otros dos tratamientos aunque las diferencias no tenían importancia clínica. Sin embargo ofreció considerables ventajas en lo relativo a una administración más fácil.

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EFFECT OF PHYSOSTIGMINE ON MORPHINE-INDUCED POSTOPERATIVE PAIN AND SOMNOLENCE

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SUMMARY

The effects of physostigmine 1 mg i.v. were studied on the analgesia, sedation and reduction in respiratory rate induced by morphine 10 mg/60 kg i.v. in 10 patients recovering from surgery. Within 5–10 min, physostigmine abolished the somnolent effect of morphine and restored the respiratory rate to pre-drug values. Analgesia, assessed by an independent observer and by the patient was, if anything, increased by physostigmine. The analeptic effect of physostigmine lasted 40–60 min.

An important factor limiting the use of morphine in acutely painful conditions is the well documented danger of significant respiratory depression. Somnolence, while less of a problem, may be a troublesome side-effect. Our previous studies in experimental animals have shown that physostigmine, an anticholinesterase agent that readily penetrates the central nervous system, can reverse the respiratory depressant effect of morphine without reducing the analgesic activity (Weinstock et al., 1980). Physostigmine was also found to antagonize the respiratory depressant effect of morphine given as part of the pre-anaesthetic medication to human subjects (Snir-Mor, Weinstock and Davidson, 1981).

These findings suggest that physostigmine may be of value in antagonizing the side-effects of morphine after surgery. However, a possible role for physostigmine in such patients would be largely vitiated if the analgesic effect of morphine was reversed.

The present study was undertaken to determine the effect of physostigmine on the somnolence induced by morphine and to clarify if it alters the level of analgesia in the postoperative period.

METHODS

The study was carried out in the postoperative ward of Hadassah University Hospital, Jerusalem, in patients recovering from abdominal surgery, who were free from cardiovascular and respiratory disease. Informed consent was obtained. Seventeen male patients were studied of whom eight underwent retropubic prostatectomy, eight inguinal herniorraphy and one lumbar sympathectomy. The age range was 42–81 yr (mean 64.9 ± 3.5) and the average weight, 72.1 ± 1.9 kg. Surgery had been carried out under lumbar extradural block. No narcotics or sedative drugs were administered before or during surgery other than diazepam 10 mg orally 90 min before operation. Thus, the subjects were free from postanaesthetic sedation and confusion which could have impaired our ability to assess the drug combination.

Our observations were commenced when the influence of the local extradural anaesthetic had waned and the patients were complaining of moderate to severe pain. The degree of pain was assessed by the patient by means of a pain chart according to the degree of severity listed on the left-hand side of table I. An independent observer who was unaware of the treatment being administered, recorded the

TABLE I. *Grading of pain severity*

Patient estimate	Pain score	Observer estimate
Very severe	5	Patient writhing, sweating and distressed
Severe	4	Patient with strained facial expression
Moderate	3	Patient still, eyes closed, face pale and avoiding movement
Slight	2	Patient dozing or asleep, colour restored
None	1	No discomfort, patient completely at ease

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degree of pain envinced by the patient according to a five-point scale as shown on the right-hand side of table I (modified from Dundee, 1980).

Patients were also rated for sedation by the independent observer according to the rating scale shown in table II. Measurements of heart rate, arterial pressure and respiratory rate were made at 10-min intervals throughout the study. After two initial assessments of pain and sedation and recordings, all patients were given droperidol (dehydrobenzperidol 2.5–5 mg i.v.) to prevent the possibility of vomiting caused by morphine or physostigmine, and the assessments were repeated 10 and 20 min later. Droperidol was selected in preference to phenothiazines because of its relatively low anticholinergic activity (Greene, 1972).

TABLE II. *Grading of sedation*

Score	Observer estimate
5	Patient does not respond to the spoken word
4	Patient responds sluggishly and relapses into sleep
3	Patient lying with eyes closed, but responds immediately when spoken to
2	Patient appears normal and alert, but does not initiate conversation
1	Patient initiates conversation and is fully aware of surroundings

Because of their relatively advanced age, six patients were given morphine hydrochloride by i.v. infusion over 5 min at a dose of 5 mg/60 kg, and this was followed 25–30 min later by a further 5 mg/60 kg. The remaining 11 patients were given morphine 10 mg/60 kg i.v. over 5 min as a single dose. Thirty minutes after the 10-mg dose or the second 5-mg dose of morphine, Scobutan (N-butylhyoscine hydrobromide 5 mg) was injected i.v. to block peripheral muscarinic cholinergic receptors. Scobutan was used rather than the more familiar atropine as there is evidence that the latter may produce prolonged sedation by blocking cholinergic transmission in pathways concerned with arousal and awareness (Longo, 1966). Furthermore atropine which, unlike Scobutan, passes the blood–brain barrier (Herz et al., 1965), may be expected to antagonize the central cholinergic effects of physostigmine. In 10 of the patients (experimental group), physostigmine salicylate, 1 mg/60 kg was given 10–15 min later by i.v. infusion over 5 min. The remaining seven patients (control group) received 2 ml of saline instead of physostigmine.

Assessments of pain, sedation, respiratory and heart rates and arterial pressure were continued for up to 45 min after the administration of physostigmine.

Scored data were analysed using the Mann–Witney test for non-parametric data. Other measurements were analysed using the paired *t* test.

RESULTS

The typical sequential responses obtained in all 10 patients to morphine and physostigmine are illustrated in figure 1 for patient no. 2 (prostatectomy). In all 17 patients morphine produced a significant

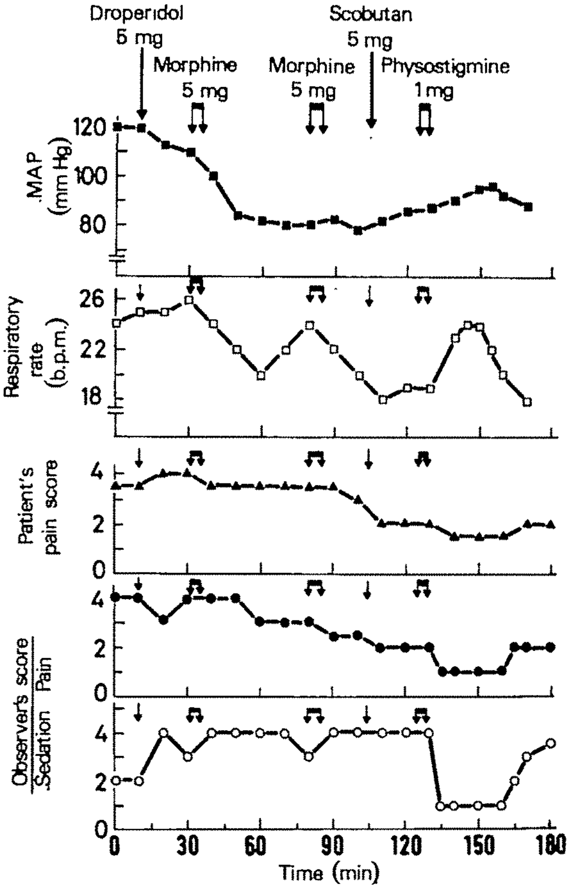

FIG. 1. The effects of morphine and physostigmine given sequentially on pain, wakefulness, respiratory rate and mean arterial pressure in one patient recovering from surgery. Droperidol and Scobutan given as bolus i.v. injections at times indicated by arrows. Morphine and physostigmine given as slow i.v. infusions during time indicated by double arrows.

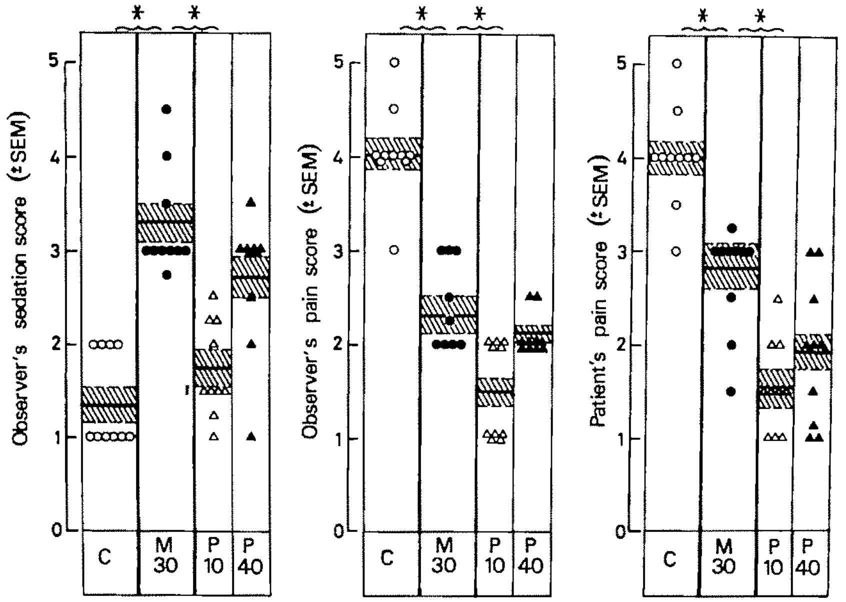

FIG. 2. The effects of physostigmine on the pain and sedation scores of the experimental group of 10 patients. C = control; M 30 = morphine 30 min; P 10 = physostigmine 10 min; P 40 = physostigmine 40 min. * Scores significantly different by Mann–Witney *U* test, $P < 0.01$. Mean score ± SEM indicated by line in hatched area.

degree of analgesia (a reduction of two points on the pain scale) 15–30 min after a total of 10 mg/60 kg had been given. This was always accompanied by marked sedation, and small but significant reductions in respiratory rate and mean arterial pressure. Droperidol caused transient sedation in five of 17 patients, but no other significant changes. Scobutan was associated with an increase in heart rate, but the pupils remained constricted, presumably as a result of morphine. No significant change was produced by saline in the observer's sedation or pain scores in the control patients, but in four of them there was a slight increase in the patient's own pain scores (table III), suggesting that the effect of morphine may have begun to decline. All 10 patients in the experimental group wakened and were able to talk coherently within 5–10 min of the infusion of physostigmine. Some described the relief of pain previously experienced and the sudden change in their state of wakefulness. Respiratory rate and the depth of tidal breathing (by observation) and arterial pressure increased after physostigmine, but there was no decrease in the degree of analgesia. Indeed, both the observer's pain score and that of the patient showed significant reduction (increased analgesia) compared with those after morphine alone (fig. 2).

The pain and sedation scores of the patients who had received physostigmine were all significantly less than those of the saline-treated controls (table III).

The effects of physostigmine had declined in all patients at 40–60 min after injection. At this time,

TABLE III. *The effect of physostigmine on analgesia and sedation induced by morphine. *Significantly less than after saline, $P < 0.01$*

	Experimental group ($n = 10$)			Control group ($n = 7$)		
	Control	Morphine (30 min)	Physostigmine (5–10 min)	Control	Morphine (30 min)	Saline (5–10 min)
Sedation score (Observer)	1.40 ± 0.16	3.25–0.16	1.73 ± 0.15*	1.28 ± 0.20	2.90 ± 0.29	2.71 ± 0.24
Pain score Observer	4.05 ± 0.16	2.35 ± 0.15	1.50 ± 0.16*	4.30 ± 0.10	2.51 ± 0.21	2.81 ± 0.29
Patient	4.00 ± 0.16	2.73 ± 0.17	1.55 ± 0.15*	4.28 ± 0.17 •	2.36 ± 0.14	2.79 ± 0.09

TABLE IV. *The effect of morphine and physostigmine given sequentially on respiratory rate, heart rate and mean arterial pressure. Values represent mean ± SEM from 10 patients. Significantly different from: control*, $P < 0.01$; morphine†, $P < 0.01$; physostigmine 10 min‡, $P < 0.05$*

Treatment	Respiratory rate (b.p.m.)	Heart rate (beat min^{-1})	MAP (mm Hg)
Pretreatment control	21.1 ± 2.1	74.6 ± 3.7	101.4 ± 5.8
Droperidol 2.5 mg, 10 min	20.4 ± 2.3	83.8 ± 4.0	93.2 ± 5.0
Morphine 10 mg, 30 min	17.6 ± 1.8*	76.8 ± 4.7	86.3 ± 3.8*
Scobutan 5 mg, 10 min	18.4 ± 1.8	97.2 ± 5.0	90.7 ± 4.5
Physostigmine 1 mg, 10 min	22.0 ± 1.6†	91.2 ± 5.1	100.6 ± 5.2†
Physostigmine 1 mg, 40 min	19.4 ± 1.7‡	86.6 ± 5.7	93.6 ± 4.8‡

the sedation and analgesia scores for morphine, together with the respiratory rates and arterial pressure, were restored to the pre-physostigmine values. The changes in respiratory rate, heart rate and arterial pressure are summarized for the experimental group of patients in table IV.

Two of the patients (herniorrhaphy and sympathectomy respectively) passed urine 15 min after the injection of physostigmine, having complained previously of urge to micturate without being able to do so. None of the patients complained of nausea or vomiting after morphine or physostigmine. Droperidol 5 mg abolished the nausea of one patient who complained of this before the assessments were commenced.

DISCUSSION

The use of extradural anaesthesia in the present study had the advantage of enabling the study to be commenced in patients who were fully aware of their surroundings. They were able to assess clearly their degree of pain and to co-operate with the investigators, in the period immediately after operation.

A total dose of morphine 10 mg/60 kg was needed in all patients to produce a reduction of the pain score from "very severe" or "severe" to "moderate-mild" pain. This degree of analgesia was accompanied in all patients by marked sedation or somnolence, and slight reductions in respiratory rate and arterial pressure.

Physostigmine, by inhibiting the inactivation of acetylcholine, leads to an accumulation of that transmitter and hence to cholinergic stimulation at both peripheral and central receptor sites. It has been found to be effective in the "anticholinergic syndrome" induced by a wide range of drugs that have cholinergic receptor blocking properties (Rumach, 1973). As opiates have been shown to inhibit the release of acetylcholine in both the central and peripheral nervous systems (Weinstock, 1971), it is a reasonable supposition that physostigmine could act as a pharmacological antidote to some of the effects of morphine.

In every patient, physostigmine reversed the sedative effect of morphine, but did not reduce the analgesia. On the basis of the observer's score, analgesia appeared even to be significantly increased by physostigmine. This, however, may merely reflect the fact that many of the patients who had previously been sleeping or lying with their eyes closed under the influence of morphine (score 2 or 3), woke up and began to talk (score 1). On the other hand, the patient pain score was also less in eight of them after physostigmine was given, and this in turn was significantly less than both pain scores in the control group. Therefore this may be an effect of physostigmine itself on pain sensation. Studies with this drug on experimental pain in animals have shown a significant analgesic effect at doses of 30–130 $\mu g\ kg^{-1}$, which results from activation of cholinergic muscarinic receptors in the central nervous system (Ireson, 1970; Dayton and Garrett, 1973). In experimental pain in human subjects, physostigmine 0.5 mg i.v. increased the threshold to varying intensities of nociceptive stimuli. This effect was associated with increased arousal in the reticular activating system and was thought to result from a dampening of the emotional component of pain (Sitaram, Buchsbaum and Gillin, 1977).

The ionized anticholinergic agent Scobutan prevented all the peripheral muscarinic effects of physostigmine, such as abdominal cramps, bradycardia, sweating or bronchial constriction, without interfering with the analeptic and respiratory stimulant effect.

Previous studies reported nausea and vomiting in a proportion of patients given physostigmine (Toro-Matos et al., 1980). The frequency of nausea and vomiting was particularly small in the study reported by Bidwai, Cornelius and Stanley (1976) when physostigmine was given to counteract somnolence induced by Innovar, which contains droperidol. In the present series, pretreatment of the patients with droperidol 2.5–5 mg also prevented these effects.

The restoration of the arterial pressure to the premorphine value by physostigmine is in accordance with previous findings in animal experiments (Weinstock, Erez and Roll, 1981). It probably results from an action of the drug in the central nervous system, via the accumulation of acetylcholine on muscarinic receptors (Varagic, 1955), since it is not shared by neostigmine which acts only on peripheral cholinesterase, and is blocked by hyoscine or atropine, which enter the central nervous system (Herz et al., 1965).

Physostigmine has been used to counteract prolonged somnolence or coma induced by different types of pharmacological agents. These include diazepam (Larson, Hurlebert and Wingard, 1977), fentanyl (Bidwai, Cornelius and Stanley, 1976), ketamine (Toro-Matos et al., 1980), tricyclic antidepressants (Burks, Walker and Rumach, 1974). All these drugs have been shown to reduce central cholinergic transmission either directly by blocking receptors of ACh (Atkinson and Ladinsky, 1972) or its release (Jhamandas, Phillis and Pinsky, 1971), or indirectly by modulating the action of other neurotransmitters such as GABA, which in turn modify cholinergic activity (Consolo, Garattini and Ladinsky, 1975).

As previously noted in our earlier study and those of others, the effect of physostigmine commences within 5–10 min and lasts 40–60 min when injected i.v. Thus, for a more prolonged reversal of the sedative and respiratory effects of morphine it may be desirable to give a constant infusion of physostigmine during the period that analgesia is required.

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EFFETS DE LA PHYSOSTIGMINE SUR L'ANALGESIE POSTOPERATOIRE ET LA SOMNOLENCE INDUITES PAR LA MORPHINE

RESUME

Nous avons étudié les effets de 1 mg de physostigmine i.v. sur l'analgésie, la somnolence et la dimunution de fréquence respiratoire induites par 10 mg de morphine i.v. pour 60 kg chez 10 patients au réveil d'un acte chirurgical. En 5–10 min, la physostimine supprimait la somnolence induite par la morphine et rétablissait la fréquence respiratoire à sa valeur d'avant l'injection de morphine. L'analgésie, évaluée par un observateur indépen-

dant et par le patient, était, si elle variait, plutôt augmentée par la physostigmine. L'effet analeptique de la physostigmine durait 40–60 min.

DIE WIRKUNG VON PHYSOSTIGMIN AUF POSTOPERATIVES SCHMERZEMPFINDEN UND SCHLÄFRIGKEIT NACH MORPHIUM

ZUSAMMENFASSUNG

Untersucht wurde die Wirkung von Physostigmin i.v. auf die durch 10 mg/60 kg Morphium i.v. hervorgerufene Analgesie, Sedierung und Herabsetzung der Atemfrequenz bie 10 Patienten. Innerhalb von 5 bis 10 min hob Physostigmin die sedierende Wirkung des Morphiums auf und stellte die normale Atemfrequenz wieder her, wie sie vor Opiatgabe bestand. Die Analgesie wurde durch einen unabhängigen Beobachter und von dem Patienten beurteilt, jedoch durch Physostigmin eher verstärkt. Die analeptische Wirkung von Physostigmin dauerte 40 bis 60 Minuten.

EFECTO DE LA FISOSTIGMINA SOBRE LA SOMNOLENCIA Y EL DOLOR POSTOPERATIVO INDUCIDOS MEDIANTE MORFINA

SUMARIO

Se estudiaron los efectos de 1 mg de fisostigmina sobre la analgesia, la sedación y la reducción del ritmo respiratorio como consecuencia de la administración intravenosa de 10 mg por 60 kg de morfina en 10 pacientes en proceso de recuperación de la intervención quirúrjica. En el plazo de 5 a 10 min, la fisostigmina neutralizó el efecto somnoliento de la morfina y restauró el ritmo respiratorio a los valores anteriores a la administración de la droga. La analgesia, si se vió afectada de alguna forma y con arreglo a lo observado por un observador imparcial, aumentó mediante la fisostigmina. El efecto analgésico de ésta duró por espacio de 40 a 60 min.

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COMPARISON OF THE EFFECTS OF ORG NC45 AND PANCURONIUM BROMIDE ON HEART RATE AND ARTERIAL PRESSURE IN ANAESTHETIZED MAN

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SUMMARY

The effects of Org NC45 and pancuronium bromide on heart rate and arterial pressure were studied in anaesthetized man. A bolus of either Org NC45 0.12 mg kg^{-1} or pancuronium 0.1 mg kg^{-1} was administered to lightly anaesthetized unstimulated subjects. Following Org NC45 heart rate decreased in the majority of subjects (mean and SEM 3.78 ± 1.36), whereas after pancuronium heart rate was increased (mean and SEM 11.91 ± 1.9). The changes in mean arterial pressure observed were minimal. The effect of endotracheal intubation on mean arterial pressure was then studied. Increase of mean arterial pressure was observed in all subjects. The increase was more marked in those patients who had received pancuronium and was significantly higher than in those patients who had received Org NC45 ($P<0.01$). We conclude that Org NC45 is devoid of vagal blocking action, and that the difference in response to the stimulus of endotracheal intubation is a result of the different effects exerted on the sympathetic nervous system by Org NC45 and pancuronium.

Org NC45 was developed as a result of pharmacological tests on the neuromuscular and autonomic blocking actions of a series of pancuronium analogues. Org NC45 was selected because it possesses negligible ganglion blocking activity, and there is a wide margin between neuromuscular and vagal blocking doses (Marshall, Agoston et al., 1980). This suggested that Org NC45 would have minimal cardiovascular side-effects, in comparison with pancuronium.

Increases in heart rate following pancuronium have usually been attributed to blockade of cardiac muscarinic receptors (Saxena and Bonta, 1970). Org NC45 is 35 times less active than pancuronium in blocking cardiac responses to vagal stimulation in anaesthetized cats (Durant et al., 1979) and 500 times less potent than pancuronium in blocking the bradycardia produced by vagal stimulation in the pithed rat (Marshall, McGrath et al., 1980).

Org NC45 also differs from pancuronium in its effects on the sympathetic nervous system. It is four times less potent as an inhibitor of the neuronal uptake of noradrenaline (Uptake$_1$) in the isolated perfused rat heart (Salt, Barnes and Conway, 1980). It is approximately 30 times less active than pancuronium in potentiating the effects of sympathetic cardioaccelerator stimulation in pithed rats and does not potentiate the cardiac effects of noradrenaline in guineapig atria (Marshall, McGrath et al., 1980).

METHODS

Fit adults gave informed consent to the study. Premedication consisted of diazepam 10 mg orally for those patients less than 70 kg in weight and 15 mg for those more than 70 kg and was administered 90 min before induction of anaesthesia. On arrival in the anaesthetic room a 22-gauge Teflon cannula (Abbocath) was inserted into the radial artery under local anaesthesia. This was connected via a pressure transducer (Hewlett–Packard 1280A) to a pen recorder (Brush Clevite). Anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen via a face-mask. Five minutes after the administration of thiopentone a bolus of either pancuronium 0.1 mg kg^{-1} (11 patients) or Org NC45 0.12 mg kg^{-1} (12 patients) was administered. Subjects were randomly assigned to these two groups.

When spontaneous ventilation ceased the lungs were ventilated artificially with 70% nitrous oxide in oxygen. Five minutes after the administration of

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the neuromuscular blocking drug a bolus of thiopentone $1.5\,\mathrm{mg\,kg^{-1}}$ was administered and the trachea intubated. Mean arterial pressure (diastolic + [systolic − diastolic]/3) and heart rate were determined in the minute before the administration of the neuromuscular blocker. This represented the control values for individual subjects. Mean arterial pressure and heart rate in the 4th minute following injection of pancuronium and Org NC45, and the peak mean arterial pressure on intubation, were determined.

RESULTS

Examples of the traces during the control period, the 4th min following injection of the neuromuscular blocking drug and the response to endotracheal intubation, are shown for two patients in the pancuronium series (fig. 1) and two patients in the Org NC45 series (fig. 2).

Heart rate

The change in heart rate for all subjects was expressed as the percentage change of the control values (fig 3). In the subjects who received Org NC 45, heart rate was increased in two (2% and 4% of control), was unchanged in two and decreased in the remainder by up to 12% of control. In absolute terms the decrease was 3.78 ± 1.36 (mean ± SEM) and this was significantly different from the control values ($P < 0.025$, *t* test). In the subjects who received pancuronium the heart rate was consistently increased. The increase in heart rate ranged from 5% of control to 30% of control. In absolute terms the increase in heart rate was 11.91 ± 1.9 (mean ± SEM) and this was significantly different from the control values ($P < 0.001$, *t* test). There was a correlation between the increase in heart rate (expressed as percentage change of control) and the control heart rate ($r = 0.635$).

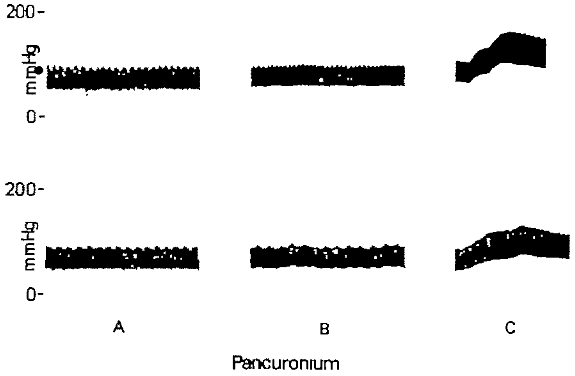

FIG. 1. The upper trace and the lower trace are recordings of arterial pressure in two different patients. Panel A = the minute before administration of pancuronium $0.1\,\mathrm{mg\,kg^{-1}}$; panel B = 4th min following injection of pancuronium; panel C = response to endotracheal intubation.

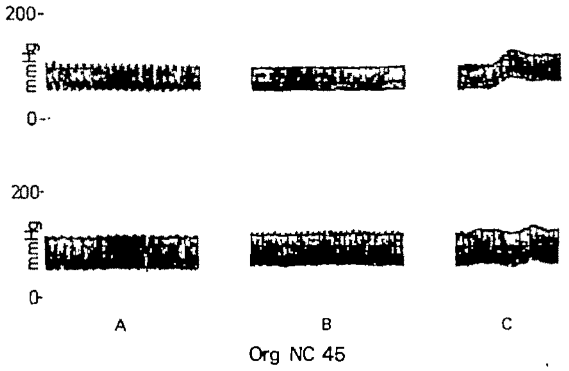

FIG. 2. The upper trace and the lower trace are recordings of arterial pressure in two different patients. Panel A = the minute before administration of Org NC45 $0.12\,\mathrm{mg\,kg^{-1}}$; panel B = 4th min following injection of Org NC45; panel C = response to endotracheal intubation.

Mean arterial pressure

Mean arterial pressure in the minute before the administration of the two drugs was not significantly different in the two groups. The mean arterial pressure at the three relevant points in the study — control, the 4th min following injection of the drugs and the peak mean arterial pressure on intubation — are shown for pancuronium and Org NC45 (fig. 4).

In the patients given pancuronium mean arterial pressure was increased in the majority (range −2.1% of control to +11.1% of control). This change in mean arterial pressure was significantly different from the control values ($P < 0.025$, *t* test). In the patients who received Org NC45, mean arterial pressure decreased in some (maximum decrease 12% of control) and was increased in others (maximum 8.8% of control). There was no statistical significance between the values after injection of the drug compared with the control values (*t* test). Mean arterial pressure was increased in all subjects as a result of endotracheal intubation. There was, however, a significantly different response in peak mean arterial pressure on intubation in those patients who had received pancuronium and Org NC45 ($P < 0.01$, *t* test and rank test). These changes in peak mean arterial pressure were expressed as percentage increase of control of each subject (fig. 5).

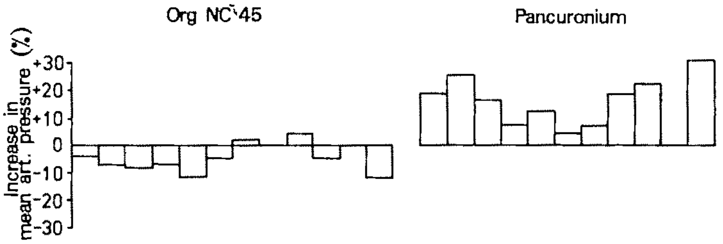

FIG. 3. Change in heart rate in the 4th min following injection of Org NC45 and pancuronium, expressed as percentages of control values.

DISCUSSION

The effect of a bolus dose of Org NC45 on heart rate in lightly anaesthetized man is different from that of pancuronium. The dose of Org NC45 used in this trial appears to be devoid of the vagal blocking action observed with pancuronium. Animal studies which have shown Org NC45 to be devoid of vagal blocking activity (Booij et al., 1980; Durant, Houwertjes and Crul, 1980), have been confirmed in man. The changes observed with pancuronium are consistent with previously reported work (Kelman and Kennedy, 1971; Miller, Eger and Stevens, 1975). When pancuronium is used in clinical practice, a stimulus that produces a sympathetic discharge results in tachycardia that would be more marked in the presence of vagal blockade. Excessive tachycardia may occur when pancuronium is used; this would be less likely to occur with Org NC45.

The effects of pancuronium and Org NC45 on mean arterial pressure seemed to be dependent on the conditions prevailing at the time the data were collected. Org NC45 did not have a consistent effect on mean arterial pressure after a bolus injection in the lightly anaesthetized unstimulated subject, and changes that did occur were minimal. The injection of pancuronium resulted in a small but significant increase in arterial pressure. This increase in mean arterial pressure did not appear to correlate with the increase in heart rate. Endotracheal intubation produced an increase in arterial pressure in all the subjects in this trial. There was, however, a difference in the pressor response to intubation between the two groups. The increase in mean arterial pressure during intubation after Org NC45 was modest and consistent. The increase in mean arterial pressure in those patients who had received pancuronium was greater and tended to be inconsistent.

In this trial an attempt was made to produce a consistent level of anaesthesia at the time of endotracheal intubation, by the careful control of the doses of anaesthetic agents used and critical timing of the manoeuvres performed. Despite this it is

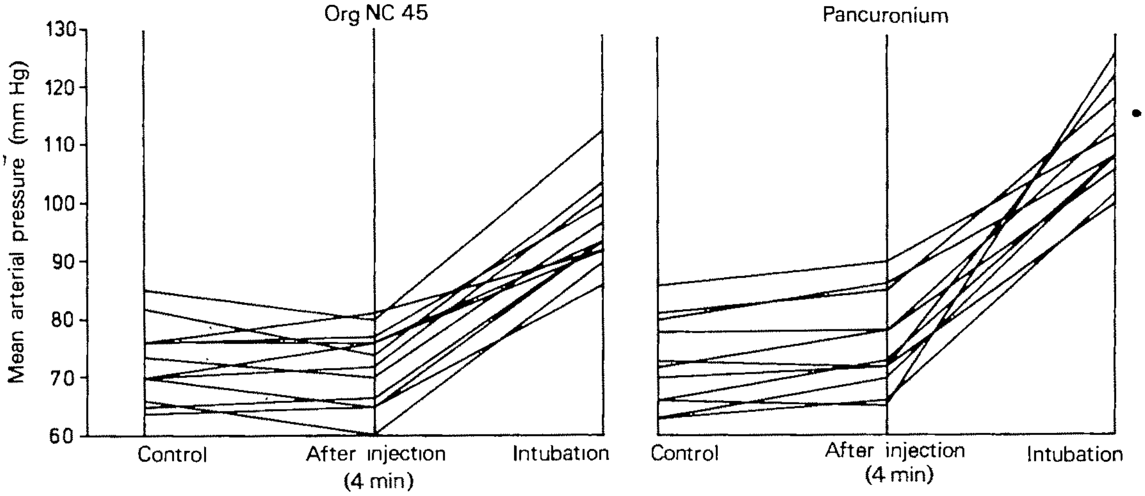

FIG. 4. Mean arterial pressure (mm Hg) during the control period, in the 4th min after injection of pancuronium 0.1 mg kg^{-1} and Org NC45 0.12 mg kg^{-1} and the peak readings on endotracheal intubation.

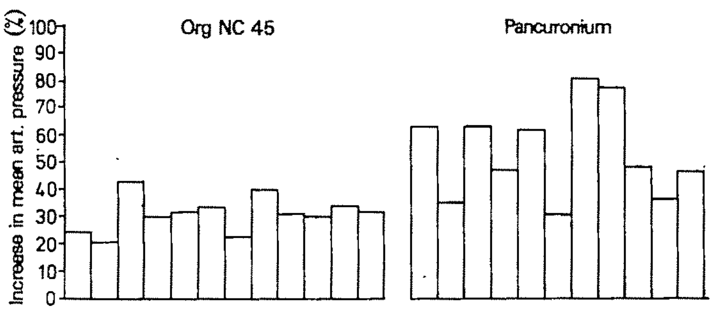

FIG. 5. Peak mean arterial pressure on endotracheal intubation. The increase in mean arterial pressure is expressed as the percentage change of control values.

impossible to be sure that all patients were at the same level of anaesthesia for the standard stimulus of endotracheal intubation. It could be anticipated, however, that the variation in level of anaesthesia would be the same in the two groups.

An explanation for the observed results may be that Org NC45 and pancuronium exert different effects on the sympathetic nervous system. Pancuronium sensitizes the sympathetic nervous system by inhibiting the reuptake of noradrenaline into sympathetic nerves. A pressor response would not be anticipated following a bolus injection of the drug. Any change in arterial pressure in an unstimulated subject could be attributed to the mild tachycardia produced by vagal blockade, although this was not the case in this trial. In the presence of a sympathetic discharge, however, an augmented response would be expected. Org NC 45 is unlikely to sensitize the sympathetic nervous system (Salt, Barnes and Conway, 1980), and one would not expect to see the exaggerated changes in mean arterial pressure during periods of sympathetic stimulation. This may explain why the two groups in this trial behaved in a similar fashion with respect to changes in mean arterial pressure after the drugs were administered, yet had a different response to endotracheal intubation.

The apparent discrepancies in the early experimental work on the cardiovascular effects of pancuronium in man (Baird and Reid, 1967; McDowell and Clark, 1969; Fastrer and Agoston, 1970; Kelman and Kennedy, 1971), may be a result of the different plans of study used and the difference in stimulation taking place during the studies, when the data were collected. In the study reported by Lyons and Clark (1972), four neuromuscular blocking drugs were studied —pancuronium, gallamine, alcuronium and tubocurarine. After injection of the drugs it was noted that pancuronium produced little change in mean arterial pressure. The fact that the greatest increase in arterial pressure in intubation 3 min after the injection of the drugs was seen with pancuronium did not receive comment.

The cardiovascular side-effects of any neuromuscular blocking drug will be dependent on the inherent pharmacological properties of the drug, and the depth of anaesthesia in relation to the surgical stimulus.

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COMPARAISON DES EFFETS DU ORG NC45 ET DU BROMURE DE PANCURONIUM SUR LA FREQUENCE CARDIAQUE ET LA PRESSION ARTERIELLE CHEZ L'HOMME ANESTHESIE

RESUME

Nous avons étudié les effets de l'Org NC45 et du bromure de pancuronium sur la fréquence cardiaque et la pression artérielle chez l'homme anesthésié. Une injection rapide de 0,12 mg kg^{-1} d'Org NC45 ou de 0,1 mg kg^{-1} de bromure de pancuronium a été faite à des sujets légèrement endormis, non stimulés. Aprés l'Org NC45, la fréquence cardiaque diminue chez la plupart des sujets (moyenne et ESM: 3,78 ± 1,76), tandis qu'elle augmente après pancuronium (11,91 ± 1,9). Les modifications de la pression artérielle moyenne observées sont minimes. On a ensuite étudié les effets de l'intubation endotrachéale sur la pression artérielle moyenne. Tous les sujets présentent une augmentation de la pression artérielle moyenne. Cette augmentation est plus marquée chez les sujets qui reçoivent du pancuronium, sujets chez qui elle est significativement plus importante que chez les sujets qui reçoivent de l'Org NC45 ($P < 0,01$). Nous en concluons que l'Org NC45 est dénué d'action parasympatholytique et que la différence de réponse au stimulus de l'intubation endotrachéale est dûe aux effets différents exercés par l'Org NC45 et la pancuronium sur le système nerveux sympathique.

VERGLEICH DER WIRKUNG VON ORG NC45 UND PANCURONIUMBROMID AUF PULSFREQUENZ UND BLUTDRUCK BEIM ANÄSTHESIERTEN PATIENTEN

ZUSAMMENFASSUNG

Die Wirkung von Org NC45 und Pancuroniumbromid auf Pulsfrequenz und arteriellen Blutdruck wurde an anästhesierten Menschen untersucht. Ein Bolus von entweder 0,12 mg kg^{-1} Org NC45 oder 0,1 mg kg^{-1} Pancuronium wurde Patienten gegeben, die sich in leichter Narkose befanden und auf die kein Reiz ausgeübt wurde. Nach Org NC45 nahm die Pulsfrequenz bei der Mehrheit der Patienten ab (Mittelwert und S.A. 3,78 ± 1,36), während sie nach Pancuronium zunahm (Mittelwert und S.A. 11,91 ± 1,9). Die Veränderungen des mittleren arteriellen Druckes varen minimal, Anschließend wurde die Auswirkung der endotrachealen Intubation auf den mittleren arteriellen Druck untersucht. In allen Fällen konnete man einen Anstieg des mittleren arteriellen Druckes beobachten. Der Anstieg war bei den Patienten, die Pancuronium erhalten hatten, ausgeprägter und signifikant höher als bei den Patienten mit Org NC45 ($P < 0,01$). Hieraus schließen wir, daß Org NC45 keine hemmende Wirkung auf den Vagus besitzt und daß die unterschiedliche Reaktion auf den Intubationsreiz auf eine Wirkung von Org NC45 und Pancuronium auf den Sympathikus zurückzuführen ist.

COMPARACION DE LOS EFECTOS DEL ORG NC 45 Y DEL BROMURO DE PANCURONIO EN EL RITMO CARDIACO Y EN LA PRESION ARTERIAL DEL HOMBRE ANESTESIADO

SUMARIO

Se estudiaron en el hombre anestesiado los efectos del Org NC45 y del bromuro de pancuronio sobre el ritmo cardiaco y la presión arterial. Se administró una dosis de 0,12 mg kg^{-1} de Org NC45 ó de 0,1 mg kg^{-1} de pancuronio a pacientes sin estimular y ligeramente anestesiados. El ritmo cardiaco disminuyó en la mayoría de los pacientes a raiz del Org NC45 (media y error típico de 3,78 ± 1,36) mientras que el ritmo cardiaco aumentó después del pancuronio (media y error típico de 11,9 ± 1,9). Los cambios que se observaron en la presión arterial media fueron mínimos. Se estudió seguidamente el efecto de la intubación endotraqueal sobre la presión arterial media. Se observó un incremento de la presión arterial media en todos los pacientes. El incremento fue más notable en aquellos pacientes que habían recibido pancuronio y fue bastante superior al de los pacientes que habían recibido Org NC45 ($P < 0,01$). Nuestra conclusión es que el Org NC45 no ejerce bloqueo vagal alguno y que la diferencia de la respuesta ante el estímulo de la intubación endotraqueal es consecuencia de los diferentes efectos que en el sistema nervioso simpático ejercen el Org NC45 y el pancuronio.

Br. J. Anaesth. (1982), 54, 441

IMPAIRED NEOSTIGMINE ANTAGONISM OF PANCURONIUM DURING ENFLURANE ANAESTHESIA IN MAN

S. DELISLE AND D. R. BEVAN

SUMMARY

We have compared the rates of recovery of pancuronium-induced neuromuscular blockade after administration of neostigmine during anaesthesia maintained with nitrous oxide and intermittent narcotics, halothane or enflurane. Thirty patients were studied in whom anaesthesia was maintained with 70% nitrous oxide in oxygen with: fentanyl or thiopentone, halothane (0.55–0.65% end-tidal), or enflurane (1.3–1.4% end-tidal). Muscle twitch response was measured using train-of-four stimulation. Pancuronium 3 mg/70 kg was antagonized with neostigmine 2.5 mg/70 kg at 10% spontaneous recovery of the first twitch of the train compared with control. There were no significant differences between the times to 10% spontaneous recovery of the first twitch or the rates of train-of-four recovery after neostigmine when the narcotic and halothane groups were compared. However, enflurane anaesthesia, in comparison with fentanyl, was associated with a significant increase in the time to 10% recovery (57.9 ± 6.0 min *v.* 35.4 ± 7.0 min) and with decreases in the train-of-four recoveries at 4, 5, 10, 20 and 30 min after neostigmine. We conclude that, under the conditions of this study, the antagonism of pancuronium-induced neuromuscular blockade with neostigmine was impaired during enflurane but not halothane anaesthesia.

Several studies have demonstrated increases in the magnitude and duration of non-depolarizing neuromuscular blockade by inhalation anaesthetics in man (Katz and Gissen, 1967; Walts and Dillon, 1970; Katz, 1971b). Potentiation of paralysis by enflurane is greater than by equipotent concentrations of halothane (Fogdall and Miller, 1975) or narcotic–nitrous oxide anaesthesia (Lebowitz, Blitt and Walts, 1970). However, the influence of enflurane anaesthesia on the antagonism of non-depolarizing block by neostigmine has not been reported.

We have studied the rates of recovery of neuromuscular activity following a standard dose of pancuronium which was antagonized by a standard dose of neostigmine at the same degree of spontaneous recovery in patients anaesthetized with equipotent concentrations of halothane or enflurane with 70% nitrous oxide. The rates of recovery have been compared with those in patients receiving nitrous oxide–narcotic anaesthesia.

METHODS

The study was approved by the hospital ethics committee. After informed consent 30 patients were studied during general surgical procedures. Their ages ranged from 27 to 77 yr (mean 55.0) and their weights from 42 to 92 kg (mean 70.1). All received atropine 0.6 mg and an opiate, pethidine 0.5–1 mg kg^{-1} or morphine 0.07–0.14 mg kg^{-1}, for premedication. All patients were free of hepatic, renal and neuromuscular disease. None had electrolyte abnormalities nor was any receiving drugs known to interfere with neuromuscular transmission.

Anaesthesia was induced with thiopentone 3–5 mg kg^{-1}, followed by suxamethonium 1 mg kg^{-1} to facilitate intubation. The patients were divided randomly into three groups, with 10 patients in each group, for maintenance anaesthesia. There were no significant differences in weights, ages or sex ratios between the groups. All patients received 70% nitrous oxide in oxygen, ventilation of the lungs was controlled and the minute volume was adjusted to maintain end-tidal carbon dioxide at 4–5% (Beckman CO_2 analyser). This was supplemented in group 1 (control) with repeated small doses of fentanyl 0.7–1.4 $\mu g\ kg^{-1}$ or thiopentone 1–2 mg kg^{-1} and in groups 2 and 3 with halothane or enflurane. Administration of the inhalation agents commenced immediately after tracheal intubation at an inspired concentration which maintained constant end-tidal concentrations of 0.55–0.65% halothane or 1.3–1.4% enflurane throughout the study, monitored with a Beckman analyser.

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After induction of anaesthesia, neuromuscular transmission was monitored continuously throughout the surgical procedure according to the method of Ali, Utting and Gray (1970). The ulnar nerve was stimulated supramaximally at the elbow using subcutaneous needle electrodes. Trains of four with square pulses of 0.2 ms duration at a frequency of 2 Hz and a train duration of 2 s were repeated every 10 s using a Grass S48 stimulator and a SIU 5 isolation unit. The hand and forearm were immobilized in a splint and the force of adduction of the adductor pollicis was measured with a force-displacement transducer (Grass F.T.10) and recorded using a pen-and-ink recorder (Grass Polygraph) at a paper speed of 50 mm min^{-1}. Pancuronium bromide 0.043 mg kg^{-1} was administered as soon as full recovery from suxamethonium was demonstrated. Thus, in those patients receiving inhalation agents pancuronium was administered 12–15 min after their commencement. After pancuronium the neuromuscular junction was allowed to recover spontaneously until the height of the first twitch of the train reached 10% of the height of the pre-pancuronium control value, when atropine 17 $\mu g\ kg^{-1}$ and neostigmine 36 $\mu g\ kg^{-1}$ were injected simultaneously. Controlled ventilation, neuromuscular transmission studies and anaesthesia with halothane or enflurane, if used, were continued for a further 30 min.

The mean values are presented with the standard error of the mean as the index of dispersion. After one-way analysis of variance, probabilities for differences between the halothane and enflurane groups were compared with the control (fentanyl) group using Student's *t* test for unpaired data. The null hypothesis was rejected when $P<0.05$.

RESULTS

Before administration of pancuronium, muscle twitch activity had returned to normal and the train-of-four (TOF)—the height of the fourth twitch as a percentage of the first in each train—was 96.9 ± 1.1, 97.5 ± 0.9 and 96.4 ± 1.1 in the fentanyl, halothane and enflurane groups respectively. The time to 10% recovery in the control (fentanyl) group was 35.4 ± 7.0 min (mean ± SEM) (table I). The time was not altered significantly by halothane (29.4 ± 4.4 min), but was prolonged by enflurane (57.9 ± 6.0 min; $P<0.05$).

Following injection of neostigmine, all patients demonstrated a rapid increase in response to the first stimulus of each train, expressed as the percentage of the first twitch height compared with control (1/C) (table I). The rates of recovery of the fentanyl and halothane groups were similar. The mean values for the enflurane group were lower than for fentanyl but the differences were not statistically significant.

Recovery of TOF showed a similar general pattern. There were no differences between the recovery rates of fentanyl and halothane, but recovery of the enflurane group was less than the control group and the differences were significant at 4, 5, 10, 20 and 30 min after reversal with neostigmine. Thus the rate of recovery of neuromuscular transmission, when assessed using train-of-four stimulation, was significantly reduced during enflurane but not halothane anaesthesia.

DISCUSSION

In general, it is assumed that "the degree of neuromuscular blockade at the time when neostigmine is administered determines the speed and extent of antagonistic action by neostigmine" (Miller, 1976). The present study indicates that the rate of recovery is reduced when neostigmine is adminis-

TABLE I. *Times (mean ± SEM) to 10% spontaneous recovery and recovery of first stimulus of each train, expressed as the percentage (± SEM) of the height of the first twitch compared with control (1/C) and of recovery of train-of-four (TOF)—the height of the fourth twitch as a percentage of the first in each train after antagonism with neostigmine.* *P <*0.05 compared with control group (fentanyl)*; **P <*0.01compared with control group (fentanyl)*

	Fentanyl (35.4 ± 7.0 min to 10% 1/C)		Halothane (29.4 ± 4.4 min to 10% 1/C)		Enflurane (57.9* ± 6.0 min to 10% 1/C)	
Time after reversal (min)	1/C	TOF	1/C	TOF	1/C	TOF
1	21.2 ±3.0	17.0 ±2.6	17.5 ±1.6	0	16.0 ±1.2	3.4 ±2.3
2	37.8 ±4.5	25.9 ±4.4	34.5 ±2.5	21.4 ±2.3	29.8 ±2.6	17.2 ±2.6
3	50.2 ±5.1	38.3 ±4.8	48.2 ±3.3	28.0 ±3.4	40.1 ±3.4	28.6 ±3.2
4	58.7 ±5.0	47.3 ±5.1	56.9 ±3.6	37.8 ±3.7	50.2 ±4.1	34.0* ±2.8
5	65.4 ±4.8	53.4 ±5.1	68.3 ±3.6	44.7 ±3.1	58.7 ±4.9	37.3* ±3.1
10	86.6 ±3.6	70.2 ±4.7	85.1 ±2.0	70.7 ±2.4	78.4 ±7.1	49.9** ±3.0
20	97.0 ±1.7	80.7 ±6.1	96.7 ±2.2	80.8 ±2.6	91.9 ±7.6	57.3** ±2.6
30	99.7 ±1.5	83.9 ±6.4	98.8 ±0.6	85.3 ±2.0	88.4 ±5.8	61.2** ±3.5

tered during enflurane anaesthesia.

Miller, Larson and Way (1972) demonstrated that the amount of neostigmine necessary to antagonize competitive neuromuscular blocking drugs was independent of the dose of relaxant administered. However, Katz (1971a) showed that, when the duration of paralysis was prolonged with a second dose of pancuronium and antagonism was attempted with neostigmine at the same degree of spontaneous recovery, subsequent recovery after neostigmine was faster in those subjects who had received the larger cumulative dose of pancuronium. These studies suggest that the rate of recovery of neuromuscular function is either unchanged or increased when the duration of the block is prolonged by increasing the dose of neuromuscular blocking drug. The present study indicates that, during enflurane anaesthesia, not only is the duration of pancuronium-induced neuromuscular blockade prolonged, but also the rate of recovery of neuromuscular activity after antagonism with neostigmine is decreased compared with patients anaesthetized with narcotics or equipotent concentrations of halothane.

In vitro studies using isolated nerve–muscle preparations have demonstrated that the predominant action of inhalation anaesthetic agents on neuromuscular transmission is upon post-junctional structures (Kennedy and Galindo, 1975a, b; Waud and Waud, 1975a, b). They induce non-competitive depression of depolarization and at equivalent anaesthetic concentrations enflurane is more depressive than halothane (Waud and Waud, 1979). In man, although there are no reports using train-of-four stimulation, the twitch response to single (Katz and Gissen, 1967) or tetanic stimuli at 30 (Lebowitz, Blitt and Walts, 1970) or 50 Hz (Fogdall and Miller, 1975) is not depressed during anaesthesia with nitrous oxide and halothane or enflurane at concentrations used in the present study. However, when the inhalation agents are combined with competitive neuromuscular blocking drugs the additive effects result in the potentiation of the relaxants (Waud, 1979).

In the present study antagonism of the neuromuscular block with neostigmine was attempted at 90% block and this level was the result of the combined effects of the anaesthetic and relaxant. It has been shown that the enhanced depression of tetanic twitch response of tubocurarine by halothane is restored to normal by neostigmine (Hughes and Payne, 1979; Payne, Hughes and Al Azawi, 1980), but the depression of single twitch response by enflurane alone could not be antagonized by neostigmine (Lebowitz, Blitt and Walts, 1970). Thus, probably, only that block from the relaxant would be reversed with neostigmine and this, in part, explains the impaired reversal of the enflurane group. In addition, Stanski and colleagues (1980) have shown a time-dependent increase in sensitivity to tubocurarine during enflurane but not halothane anaesthesia. If the same phenomenon occurs with pancuronium it would also contribute to the impaired antagonism.

During the course of the present study the concentration of anaesthetic agent in the muscles would have increased gradually and the effect on neuromuscular conduction would have been greater during enflurane than halothane anaesthesia for several reasons. Enflurane is a more potent depressant of neuromuscular conduction (Waud and Waud, 1979) and muscle equilibrium would have been greater as a result of its longer administration and lower muscle solubility (Eger, 1974). Simple calculations show that the muscle anaesthetic concentration at the end of the study would have reached approximately 80% of the end-tidal concentration in the enflurane group but only 50% in the halothane group.

Patients anaesthetized with halothane showed no difference in duration or antagonism of neuromuscular blockade compared with those receiving fentanyl. This does not deny any action of halothane on neuromuscular transmission, because differences might have been seen if spontaneous recovery had been observed for longer. In addition preliminary studies in animals suggest that fentanyl may have a similar small potentiating effect (Krieg et al., 1980).

Impaired neostigmine antagonism of a non-depolarizing neuromuscular blockade, as opposed to potentiation of its intensity and duration has only been proved in association with hypercapnia (Miller et al., 1975; Miller and Roderick, 1978; Tammisto, Wirtavouri and Salmenperä, 1981), metabolic alkalosis (Miller et al., 1975; Miller and Roderick, 1978) and antibiotic administration (Miller, 1976). Enflurane anaesthesia should be added to this list. However, the results of this study were obtained under standardized experimental conditions. In the clinical situation, reversal may be attempted at different, usually greater, degrees of spontaneous recovery of neuromuscular activity and the inhaled concentration of enflurane reduced before the end of surgery. Both of these would reduce the effects of the changes described.

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ALTERATION DE L'ANTAGONISME DU PANCURONIUM PAR LA NEOSTIGMINE AU COURS DE L'ANESTHESIE A L'ENFLURANE CHEZ L'HOMME

RESUME

Nous avons comparé les vitesses de récupération d'un bloc neuromusculaire induit par le pancuronium après administration de neostigmine au cours d'une anesthésie entretenue par le protoxyde d'azote et soit des morphinomimétiques administrés en discontinu, soit de l'halothane, soit de l'enflurane. Nous avons étudié 30 patients chez qui l'anesthésie générale était entretenue soit avec du protoxyde d'azote (70%), du fentanyl et du thiopental, soit du protoxyde d'azote (70%) et de l'halothane (0,55–0,65% en fin d'expiration), soit du protoxyde d'azote (70%) et de l'enflurane (1,3–1,4% en fin d'expiration). La réponse musculaire du twitch était mesurée en utilisant la stimulation par le train de quatre. On antagonisait l'action du pancuronium (3 mg/70 kg) par de la néostigmine (2,5 mg/70 kg), à 10% de récupération spontanée du premier twitch du train par rapport à la valeur contrôle, lorsque l'on comparait les groupes avec morphinomimétiques et avec halothane. Il n'y avait pas de différence significative entre les délais d'obtention d'une récupération spontanée de 10% et les vitesses de récupération du train de quatre après néostigmine. Par contre, si on la compare à l'anesthésie entretenue au fentanyl, l'anesthésie à l'enflurane s'accompagne d'un allongement significatif du délai de récupération de 10% (57,9 ± 6,0 min contre 35,4 ± 7,0 min) et d'une décroissance dans les récupérations du train de quatre à 4, 5, 10, 20 et 30 min après néostigmine. Nous en concluons que, dans les conditions de cette étude, l'antagonisme, par la néostigmine, du bloc neuromusculaire induit par le pancuronium est altéré par l'anesthésie à l'enflurane mais pas par l'anesthésie à l'halothane.

ABGESCHWÄCHTE ANTAGONISIERENDE WIRKUNG VON NEOSTIGMIN AUF PANCURONIUM UNTER ENFLURANE-ANAESTHESIE BEIM MENSCHEN

ZUSAMMENFASSUNG

Wir haben die Erholungszeit einer durch Pancuronium hervorgerufenen neuromuskulären Blockade nach Gabe von Neostigmin bei Narkosen verglichen, die mit Lachgas/Sauerstoff entweder mit i.v. Narkotika oder mit Halothan bzw. mit Enflurane unterhalten wurden. Wir untersuchten 30 Patienten, die eine Narkose mit N_2O 70%–Fentanyl/Thiopental bzw. mit N_2O 70%–Halothan (0,55 ± 0,6%) oder mit N_2O 70%–Enflurane (1,3 ± 4%) erhielten. Die Muskelkontraktilität wurde mit der "train-of-four"-Methode gemmessen. Pancuronium (3 mg/70 kg) wurde mit Neostigmin (2,5 mg/70 kg) antagonisiert, wenn eine 10% ige Spontanerholung der ersten Kontraktilität im Vergleich zur Kontrollgruppe eingetreten war. Es gab keinen signifikanten Unterschied zwischen der Zeit einer 10%igen Spontanerholung, der ersten Kontraktilität und den Zeiten der

"train-of-four"-Erholung nach Neostigmin im Vergleich der i.v. Narkotika und der Halothan-Gruppe. Unter Enfluran-Narkose zeigte sich jedoch im Vergleich zu Fentanyl ein deutlicher Anstieg der 10%-Erholungszeit (57,9 ± 6,0 min *vs.* 35,4 ± 7,0 min) und Abnahme der "train-of-four"-Zeiten 4, 5, 10, 20 und 30 min nach Neostigmin-Gabe. Daraus schließen wir, daß die antagonisierende Wirkung von Neostigmin auf die durch Pancuronium ausgelöste neuromuskuläre Blockade bei Enflurane-Narkose abgeschwächt ist. Bei Halothan ist dies jedoch nicht der Fall.

IMPOSIBILIDAD DE NEUTRALIZAR EL PANCURONIO CON NEOSTIGMINA DURANTE LA ANESTESIA EN EL HOMBRE MEDIANTE ENFLURANO

SUMARIO

Hemos comparado los regímenes de recuperación del bloqueo neuromuscular inducido por pancuronio, después de la administración de neostigmina y durante la anestesia mantenida con óxido nitroso y narcóticos administrados intermitentemente, bien fuera halotano o enflurano. Se estudiaron treinta pacientes en los que la anestesia se mantuvo con óxido nitroso lá 70% en fentanilo y tiopentona, con óxido nitroso al 70% en halotano (periodo final de 0,55 – 0,65%) o con óxido nitroso al 70% en enflurano (periodo final de 1,3 – 1,4%). Se midió la respuesta de crispamiento muscular usando estimulación de cuatro impulsos. El pancuronio 3 mg/70 kg se neutralizó con neostigmina 2,5 mg/70 kg al acontecer una recuperación espontánea del 10% correspondiente al primer impulso, en comparación con el control. No hubo diferencias notables en los periodos de tiempo necesarios para obtener el 10% de recuperación espontánea correspondientes a la primera crispación, ni en los regímenes de recuperación de los cuatro impulsos después de administrar la neostigmina, cuando se compararon los grupos de narcóticos y los de halotano. Sin embargo, la anestesia con enflurano, en comparacón con la de fentanilo, vino asociado con un incremento significativo del periodo necesario para obtener la recuperación del 10% (57,9 ± 6,0 min contra 35,4 ± 7,0 min) y con disminuciones de las recuperaciones de los cuatro impulsos, a los 4, 5, 10, 20, y 30 minutos después de la neostigmina. Concluimos que bajo las condiciones de este estudio, la neutralización del bloqueo muscular inducido por pancuronio mediante la neostigmina se vió imposibilitada dutante la anestesia con enflurano pero no durante la de halotano.

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RECOVERY FROM DAY-CASE ANAESTHESIA

Comparison between methohexitone, Althesin and etomidate

J. CRAIG, G. M. COOPER AND J. W. SEAR

SUMMARY

One hundred unpremedicated patients, undergoing short gynaecological procedures, were randomly allocated to receive one of three i.v. hypnotic agents (methohexitone, Althesin and etomidate) alone or in combination with fentanyl, to supplement 66% nitrous oxide in oxygen. Recovery was assessed by the time patients took to open the eyes, to give correct date of birth, to achieve a certain level of manipulative skill with a children's post-box toy, and to perform a paper and pencil test. Satisfactory operating conditions were not obtained using etomidate alone. Administration of methohexitone alone resulted in a more rapid initial awakening than Althesin alone ($P<0.05$) and the administration of fentanyl with methohexitone reduced the total dose given of the latter ($P<0.01$). Administration of fentanyl with Althesin or methohexitone did not significantly prolong the "post-box" recovery time. Side-effects were less common with Althesin, with or without fentanyl and etomidate with fentanyl was associated with the greatest frequency of complications.

The increasing need for outpatient surgical procedures requires anaesthetic techniques providing rapid recovery with minimal side-effects. For short gynaecological procedures the intermittent administration of an i.v. hypnotic with or without a narcotic supplement is common practice, whilst the use of volatile agents for procedures such as surgical termination of pregnancy is subject to debate (Grant, 1980). The three i.v. hypnotic agents used in this study are rapidly cleared from the blood and degraded to inactive metabolites. They are, therefore, considered suitable for day-case surgery (Carson, Graham and Dundee, 1975; Miller, Hendry and Lees, 1978). The synthetic short-acting narcotic, fentanyl, is often added to improve the quality of anaesthesia.

As a rapid return to wakefulness is required, specific recovery times were measured in assessing these anaesthetic techniques.

PATIENTS AND METHODS

The patients studied were aged between 16 and 50 yr and were fit apart from their gynaecological problems. All gave their informed consent to the studies. No premedication was given. They all underwent a short procedure involving dilatation of the cervix, which acted as a standard surgical stimulus.

The patients were randomly allocated to one of five groups. Groups A and B received methohexitone 1.5 mg kg^{-1} with increments of 10 mg. Groups C and D received Althesin 0.6 mg kg^{-1} total steroid with increments of total steroid 6 mg, and group E received etomidate 0.3 mg kg^{-1} with increments of 2 mg. Groups B, D and E received fentanyl 100 μg i.v. immediately before the induction dose. The technique of intermittent etomidate without fentanyl was abandoned after a pilot study of six patients, as it was found to provide unsatisfactory surgical conditions because of excessive muscular activity. No other drug was given with the exception of Syntocinon (5 units) to those patients undergoing vaginal termination of pregnancy. The patients were visited before operation, when the control pre-anaesthetic values of the recovery tests were obtained.

Two tests were used to assess recovery. The first, based on the peg-board described by Vickers (1965), involved the use of a Kiddicraft post-box toy. Eighteen shapes, three each of six different types, were available for "posting" through corresponding holes in the lid of the toy. The number of shapes posted in 20 s was noted after the patient had practised to achieve a consistent result. The second test was the deletion of the letter *p*, described by Dixon and Thornton (1973). The patient was presented with a foolscap sheet containing 58 lines of 36 close-spaced letters, and asked to delete as many letters *p* as possible without omissions in 3 min. This was performed twice before operation, and the score of the

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better attempt noted, as judged by the number of lines completed and errors made.

Anaesthesia was induced with the i.v. hypnotic given over 30 s, with those randomly allocated receiving fentanyl 100 μg just before the induction agent. Anaesthesia was maintained with 66% nitrous oxide in oxygen given from a face-mask via a Magill circuit (fresh gas flow 6 litre min^{-1}), supplemented by increments of the hypnotic given when clinically indicated by patient movement. At the end of surgery, nitrous oxide was discontinued and the time noted.

The patient was observed in the recovery ward by an independent anaesthetist who was unaware of the technique used. The times taken for the patient to open her eyes on command, and to give her correct date of birth were noted. When sufficiently awake to sit up on the trolley, the patient was asked to perform the post-box test. This was repeated every 5 min until she was able to "post" her control (pre-anaesthetic) number of shapes in 20 s. On achieving this, she was asked to perform the deletion of *p* test once more (wearing spectacles if these had been worn before operation).

Troublesome side-effects of the anaesthetic were noted and the patients specifically asked about pain at the injection site. If required to suppress nausea, metoclopramide 10 mg was administered i.v. by the observing anaesthetist.

A comparable group of 20 healthy females not receiving anaesthesia was also tested with the post-box. When they repeated the test 1 or 2 h later, the number of attempts required to achieve their original score was noted.

RESULTS

The twenty patients in each group were comparable in respect of age, weight and height (table I). The duration of anaesthesia was approximately 9 min in each group. The total doses of methohexitone and Althesin were decreased by the addition of fentanyl (29% and 12% respectively), the former being significant at the 1% level ($t = 3.599$). Similar numbers of patients in each group received Syntocinon.

Looking at the pattern of recovery, we would expect to find a skewed distribution as no patient would be able to perform any of the tests before the end of the anaesthetic. The majority would perform tests within a short time, but a few would have a prolonged recovery time whether for opening eyes, giving date of birth or performing the post-box test. In fact we found a skewed distribution for all indices of recovery and statistical analysis was then performed on logarithmically transformed data (table II).

There was no difference between groups A and C in the time the patients took to open their eyes, but orientation to giving correct date of birth was more rapid in those receiving methohexitone alone ($P < 0.05$). This was not reflected in the post-box test, however, in which there was no significant difference between A and C. Group C showed less variability with narrower 95% confidence limits.

The addition of fentanyl (groups B and D) did not significantly alter the recovery times of the post-box test, even though the dose of methohexitone given was significantly less than in group A. The group (E) who received etomidate and fentanyl took longer to complete the post-box test when compared with the two non-fentanyl groups ($P < 0.01$ and $P < 0.001$, groups A and C respectively), but not when compared with groups B and D.

Table III shows the pre- to post-operative changes in the scores of the letter deletion test. We were unable to detect any change in the ability to perform this test in patients immediately after completion of the post-box test, and none of the groups differed significantly from each other using non-parametric testing (Wilcoxon Rank Sum test).

In the control group of 20 age-matched healthy

TABLE I. *Patient age, weight and height of the groups, and the duration of anaesthesia and total dose of hypnotic agent (means + SEM)*

	A	B	C	D	E
Age (yr)	30.6± 2.5	36.2±2.2	28.9±2.2	33.4±2.5	31.6±2.0
Weight (kg)	60.9± 2.1	59.1±2.0	57.5±1.9	61.9±2.2	58.4±1.6
Height (cm)	154.0± 2.0	154.0±1.0	154.0±2.0	156.0±1.0	156.0±1.0
Duration (min)	9.4± 0.6	8.4±0.4	9.0±0.7	8.5±0.7	9.0±0.7
Total dose (mg)	178.0±12.0	128.0±7.0	62.0±3.0	55.0±3.0	24.0±1.0

TABLE II. *The mean values of the three indices of recovery in minutes ± 95% confidence limits (*P<0.05; **P<0.01; ***P<0.001*

	A	B	C	D	E
Time to open eyes (min)	2.6 (0.6–10.1)	1.5 (0.2–14.2)	1.9 (0.8–10.7)	2.7 (0.5–13.3)	2.1 (0.4–10.3)
	*			*	
Time to give correct birth date (min)	3.8 (1.3–11.6)	2.5 (0.9– 7.5)	6.3 (1.2–33.0)	5.7 (1.3–25.2)	3.9 (0.9–16.9)
		*			
			**		
				***	
Time to complete post-box test (min)	43.8 (12.0–160.0)	56.4 (16.0–198.1)	43.0 (22.1– 83.6)	51.7 (15.0–178.4)	76.2 (29.2–199.0)

females not undergoing anaesthesia or surgery, repeat testing 1.5–2 h later showed that they all achieved their test performance with the post-box within one to four attempts. The majority of subjects (95%) attained their target at the first or second attempt.

The least number of complications was seen with Althesin (groups C and D) ($P<0.01$). One additional complication indicated in group D (table IV) was an anaphylactic reaction to Althesin, with evidence of complement C_3 conversion and C_4 depletion. These changes indicate complement activation and consumption via the classical pathway, which is the usual mechanism of adverse reactions to Althesin on repeat exposure. The re-exposure of this patient was inadvertent, as the patient denied having received previous anaesthesia at the preoperative visit. Subsequent questioning gave a history of anaesthesia for a previous termination of pregnancy.

Pain on injection was common when either methohexitone or etomidate was used, and hiccup was more common in the methohexitone groups. Nausea and vomiting occurred more frequently in those groups of patients receiving fentanyl ($\chi^2 = 11.27$; $P<0.001$ (χ^2 test with Yate's correction for small numbers)). The overall number of complications was greatest in those patients receiving etomidate and fentanyl (group E).

TABLE III. *The mean pre- to post-operative changes in the deletion of p test scores (compared using Wilcoxon signed rank test on paired data; no statistically significant differences)*

	A	B	C	D	E
Errors	+2.6	−0.1	+0.6	+0.2	−1.3
Wilcoxon rank sums	62.0	84.0	81.0	88.7	60.0
Lines	0.0	−2.0	+0.9	−1.7	−1.6
Wilcoxon rank sums	80.5	40.0	71.5	57.0	59.0

DISCUSSION

Many tests have been described to assess recovery, some of which are time-consuming and may require the use of expensive or elaborate equipment (Green et al., 1963; Doenicke, Kugler and Laub, 1967; Laborit, Angiboust and Papin, 1975). Korttila has described a battery of tests to assess various stages of recovery, culminating in the fitness to drive (Korttila et al., 1975; Kortilla, 1976).

We have looked for a test which could be performed frequently in order to obtain a definite clinical end-point, in preference to testing at a fixed time interval after the end of anaesthesia and surgery. The post-box toy assesses a certain level of manual dexterity, spatial orientation and hand–eye co-ordination, for which the patients act as their own controls. Their stage of recovery is also reflected in their ability to perform the paper-and-pencil test described, which requires a more prolonged period of concentration.

Patients may waken and become orientated more quickly after one anaesthetic than after another and this will be important in the recovery room. How-

TABLE IV. *Numbers of patients in the five groups experiencing complications* (n = 20 *patients*)

	A	B	C	D	E
Pain on injection	7	6	0	0	8
Hiccup	7	7	0	1	0
Nausea and vomiting	3	7	1	2	15
Total with complications	14	13	1	4	17

ever, this may not be reflected in the speed of recovery for more complex tasks which are appropriate for consideration in discharging patients home. Although we are not able to indicate if the level of recovery, as assessed by this toy, represents patient fitness for discharge home, the skills enumerated are of relevance. Indeed, we saw that, although Group C who received Althesin alone were the slowest to orientate in giving their correct date of birth, they were the group to achieve the most rapid (43 min) and reliable (the narrowest confidence limits) recovery.

Patients in group E were slower to perform the post-box test than groups A and C, although not significantly slower than the other two groups who had received fentanyl. The etomidate and fentanyl technique was also associated with a greater frequency of complications, especially nausea and vomiting which would make early discharge from hospital difficult. The most serious complication was the anaphylactic reaction to Althesin and the risks of such a reaction must be weighed against its possible advantages.

Metoclopramide was given after operation to those patients who were unable to carry out the post-box test because of nausea and vomiting. The alleviation of these symptoms allowed all patients subsequently to complete the tests. We do not know if the use of this centrally active anti-emetic had any effect on the time to completion of the tests.

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REVEIL D'UNE ANESTHESIE AMBULATOIRE: COMPARAISON ENTRE LA METHOHEXITONE, L'ALTHESIN ET L'ETOMIDATE

RESUME

Une centaine de patientes non prémédiquées, subissant des actes gynécologiques courts, ont reçu au hasard l'un des trois agents anesthésiques intraveineux (méthohexitone, Althésin et étomidate) seul ou associé à du fentanyl, comme adjuvant de 66% de protoxyde d'azote dans l'oxygène. Nous n'avons pas obtenu de conditions opératoires satisfaisantes en utilisant l'étomidate seul. Le réveil était estimé sur le temps que les patientes mettaient à ouvrir les yeux, à donner correctement leur date de naissance, à atteindre un certain niveau d'habileté manuelle dans la manipulation d'une boîte à lettre d'enfant, et à répondre à un test utilisant papier et crayon. L'administration de méthohexitone seule entrainait un réveil initial plus rapide que l'Althésin seule ($P < 0,05$), et l'administration de fentanyl avec la méthohexitone diminuait la dose totale utilisée de ce dernier produit ($P < 0,01$). L'administration de fentanyl avec l'Althésin ou la méthohexitone ne prolongeait pas significativement le délai d'exécution correcte du test de la 'boîte à lettre'. Les effets secondaires étaient moins importants avec l'Althésin avec ou sans fentanyl, et l'étomidate associé au fentanyl entrainait le plus grande fréquence de complications.

ERHOLUNGSPHASE NACH AMBULANTER ANÄSTHESIE: VERGLEICH VON METHOHEXITAL, ALTHESIN UND ETOMIDATE

ZUSAMMENFASSUNG

Hundert nichtprämedizierte Patientinnen, die sich einem kurzen gynäkologischen Eingriff zu unterziehen hatten, erhielten nach Randomisierungsplan eines der drei i.v. Hypnotika (Methohexital, Althesin und Etomidate) entweder alleine oder in Kombination mit Fentanyl. Zusätzlich wurde 66% Lachgas/Sauerstoff gegeben. Mit Etomidate allein wurden keine zufriedenstellenden Operationsbedingungen erzielt. Das Erwachen wurde danach beurteilt, wie lange die Patientinnen brauchten, um fähig zu sein, die Augen wieder zu öffnen, ihr Geburtsdatum richtig anzugeben, eine gewisse Geschicklichkeit im Umgang mit einem Kinderbriefkasten zu zeigen und einen Test mit Bleistift und Papier zu bestehen. Methohexital allein führte zu schnellerem Erwachen als Althesin allein ($P < 0,05$). Die gleichzeitige Gabe von Fentanyl und Methohexital ermöglichte es, die Gesamtdosis von Methohexital zu reduzieren ($P < 0.01$). Die Gabe von Fentanyl mit Althesin oder Methohexital verlängerte nicht signifikant die "Spielzeug-Briefkasten"-Aufwachzeit. Nebenwirkungen traten bei Althesin seltener auf mit und ohne Fentanyl. Die Kombination Etomidate/Fentanyl brachte die meisten Komplikationen mit sich.

RECUPERACION DESPUES DE LA ANESTESIA EN UN DIA FACULTATIVO ESTUDIO COMPARATIVO ENTRE LA METOHEXITONA, LA ALTESINA Y LA ETOMIDATA

SUMARIO

Se asignaron de forma aleatoria 100 pacientes no premedicadas a las que se iba a someter a breves procedimientos ginecológicos, de forma que se las administrara uno de los tres agentes hipnóticos de carácter intravenoso (metohexitona, Altesina y etomidata), por sí sólo o en combinación con fentanilo, para suplementar el 66% de óxido nitroso en oxígeno. La recuperación se evaluó mediante el tiempo que las pacientes necesitaron para abrir los ojos, para dar su fecha de nacimiento correctamente, para conseguir un cierto grado de destreza manual con un buzón de correos de juguete y para ejecutar una prueba con papel y lapiz. No se obtuvieron condiciones de trabajo satisfactorias al usar sólo etomidata. La administración de metohexiotna por sí sóla produjo un despertar inicial más rápido que la Altesina sóla ($P < 0,05$) y la administración de fentanilo con metohexitona redujo la administración total de esta última ($P < 0,01$). La administración de fentanilo con Altesina o con metohexitona no prolongó de forma significativa el periodo de recuperación relativo al "buzón de correos". Los efectos secundarios fueron menos corrientes con la Altesina, con fentanilo o sin él, y la combinación de etomidata con fentanilo vino asociada con la mayor frecuencia de complicaciones.

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SORE THROAT AFTER OPERATION: INFLUENCE OF TRACHEAL INTUBATION, INTRACUFF PRESSURE AND TYPE OF CUFF

P. J. JENSEN, P. HOMMELGAARD, P. SØNDERGAARD AND S. ERIKSEN

SUMMARY

One hundred and eighty-four patients were studied to elucidate the contribution of intracuff pressure and cuff type to the occurrence of sore throat and hoarseness after operation. The patients were allocated to one of the following groups: A = mask only; B = reusable Rüsch tube with intermittent cuff volume adjustment; C = reusable Rüsch tube without cuff volume adjustment; D = disposable Portex Blue Line tube with intermittent cuff volume adjustment; E = disposable Shiley Low Pressure tube with intermittent cuff volume adjustment. Nitrous oxide was a component of anaesthesia in all patients. Moderate or severe symptoms were recorded in 30–33% of the patients in groups C, D and E, contrasting with group B, in which these sequelae were seen in only 10% of patients ($P < 0.025$). All sequelae occurred less frequently in group A than in any of the other groups ($P < 0.025$). Women were more likely to develop sore throat after intubation than were men ($P < 0.01$). A possible relationship between differences in cuff–trachea contact area is postulated.

Complications of long-term tracheal intubation are well known and are often related to reductions in blood-flow in the tracheal mucosa induced by cuff to tracheal wall pressures exceeding 30 mm Hg (Nordin, Lindholm and Wolgast, 1977; Bergström, 1978). Short-term intubation with cuffed tubes is followed by sore throat and hoarseness in 24–65% of patients (Loeser et al., 1976; Loeser, Machin et al., 1978a). Recent investigations have demonstrated that low residual volume cuff tubes cause the least occurrence and severity of postoperative sore throat, possible because the cuff–tracheal surface contact area is smallest when these tubes are used (Loeser, Bennett et al., 1980). The present study was undertaken to confirm the above mentioned findings and possibly relate the clinical results to measurements of cuff–contact area in an experimental model.

PATIENTS AND METHODS

Postoperative sore throat was evaluated in 184 adult patients aged 17–75 yr who had undergone abdominal, gynaecological or limb operations. The patients were allocated to one of the following groups: A = mask anaesthesia—no intubation ($n = 22$); B = intubation with Rüsch Red Rubber, intermittent intracuff volume adjustment to "just seal" ($n = 40$); C = intubation with Rüsch Red Rubber, slight to moderate excess of air in cuffs, no adjustment ($n = 42$); D = intubation with Portex Blue Line, intermittent intracuff volume adjustment to just seal the airway ($n = 40$); E = intubation with Shiley Low Pressure, intermittent intracuff volume adjustment to just seal the airway ($n = 40$).

All patients were in the supine position. Patients who needed a nasogastric tube or oropharyngeal airway, those in whom tracheal intubation required more than one attempt or who coughed after intubation or before extubation, were excluded from the study. In no instances were supplementary operations on head, neck and mouth performed.

The patients were premedicated with either morphine and hyoscine or pethidine and atropine. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} after precurarization and administration of a small dose of atropine i.v. Neuromuscular blockade was achieved with suxamethonium 100 mg and the trachea intubated with endotracheal tubes sizes 7.5–9.0 mm according to the anaesthetist's judgement. The endotracheal tubes were lubricated with a standard jelly without local analgesic. Cuffs were filled with room air.

Anaesthesia was maintained with halothane, or as a balanced procedure, with 67% nitrous oxide in oxygen. Neuromuscular blocking drugs were used if required for the surgical procedure. All patients had a small intradental gauze roll in place throughout the operation. Extubation was accomplished in the

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operating room after necessary clearance of secretions and after the ability to maintain head-lift was secured.

Ventilation was assisted in group A and controlled in groups B–E. Intracuff pressures were measured towards the end of operation with either a high pressure manometer (Siemens Elema) or a low pressure manometer (Portex). Corrections were made for apparatus compressible volume in the high pressure readings.

Intracuff volume was adjusted each 15 min in groups B, D and E to the point where no leakage was found during the end-inspiratory phase. In group C, a small volume of room air in excess of what was needed to establish a seal was used.

The patients were allowed to drink when awake and when pharyngeal activity was restored. Pethidine was given i.m. after operation when required.

All patients were interviewed 24–30 h after operation by an anaesthetist who was unaware of the group to which the patient belonged. A questionnaire evaluating the frequency and severity of sore throat and placing these complaints relative to others in the period immediately after operative (pain, nausea, vomiting) was used. Patient responses were graded on a 0–3 scale as follows:

0 = no sore nor irritable throat and no evidence of hoarseness;
1 = minimal sore or irritable throat, no hoarseness;
2 = moderate sore throat, slight hoarseness;
3 = severe sore throat, obvious hoarseness.

In addition to the clinical investigation, six 7.5-mm tubes of each variety studied were evaluated in an artifical trachea to determine cuff–tracheal wall surface contact area during cuff inflation. Sections of heavy cardboard tubes of 1.6, 1.8 and 2.0 cm diameter were used as artificial tracheae. The cuffs were inflated until a seal withstanding 20 cm H_2O pressure was established. Enamel aerosol paint was then sprayed into the tubes from each side, outlining the surface contact area. The length of the area was measured and the total area calculated. An additional group of high pressure readings simulating group C patients was established by the use of Rüsch Red Rubber tubes with cuffs inflated to an intracuff pressure approximately 100 cm H_2O in excess of what was needed to establish the seal.

The Chi square test with Yates' correction was used in comparing the frequency of sore throat. The Mann–Whitney test was used to compare the average score as expression of severity of sore throat. $P < 0.05$ was regarded as statistically significant.

RESULTS

Duration of operation, sex and age distribution and types of operative procedures were similar in groups B–E. Patients anaesthetized with a mask technique had a shorter duration of operation (82 min *v.* 115 min). The percentage of men in this group was greater than in the intubation groups (55% *v.* 28%).

The average score expressing the severity of sore throat was lower in the mask and Rüsch low pressure groups than in groups C–E, although statistically significant differences can only be demonstrated between group A and groups C–E ($P < 0.05$) (table I). The total frequency of sore throat was significantly less in group A than in any other group ($P < 0.025$). When this frequency was analysed according to severity it was seen that slight changes (score 1) were least pronounced in group A. The difference between group A and groups B, D and E was statistically significant ($P < 0.05$), whereas the differences between A and C and between C and B, D, E were insignificant. In comparing the more severe examples of sore throat (scores 2 and 3)

TABLE I. *Frequency and severity of sore throat after operation. Intracuff pressure towards end of operation (mean ± SEM)*

				Frequency		
	n	Intracuff pressure (cm H_2O)	Average score	(%)	Score 1 (%)	Score 2+3 (%)
Mask	22	—	0.32	18	9	9
Rüsch Red Rubber						
"Low"	40	218 ± 10	0.58	45	35	10
"High"	42	306 ± 8	0.86	52	20	32
Portex Blue Line	40	88 ± 8	1.08	63	30	33
Shiley LP	40	18 ± 2	1.03	65	35	30

TABLE II. *Comparison between results from clinical and experimental studies (Mean ± SEM)*

	Experimental study				Clinical study		
	n	Intracuff pressure (cm H_2O)	Cuff length (mm)	Contact area (mm^2)	n	Average score	Intracuff pressure (cm H_2O)
Rüsch Red Rubber							
"Low"	18	326 ± 12	21 ± 0.5	1187	40	0.58	218 ± 10
"High"	17	435 ± 20	24 ± 0.8	1356	42	0.86	306 ± 8
Portex Blue Line	18	88 ± 5	24 ± 0.6	1356	40	1.08	88 ± 8
Shiley LP	18	13 ± 1	34 ± 0.9	1922	40	1.03	18 ± 2

it was seen that groups A and B (mask and Rüsch low pressure) differed from groups C, D and E ($P < 0.025$). Women were more likely to develop sore throat or hoarseness after intubation than were men (63% *v.* 39%) ($P < 0.01$). Of 184 patients investigated, a total of 95 complained of sore throat. However, only five of these patients claimed that their main complaint was sore throat or hoarseness.

Table II indicates that the smallest cuff length found in the experimental design was in the Rüsch low pressure group. The lowest average score in the clinical investigation was found in the corresponding group. The average scores were increased in the other groups corresponding to an increase in experimental cuff length.

DISCUSSION

It has been shown (Loeser et al., 1976) that the frequency and severity of postoperative sore throat after short-term intubation was significantly greater after the use of low-pressure, high-volume cuffs, than after the use of a mask or of high-pressure, low-volume cuffs. This phenomenon is surprising in as much as low-pressure cuffed endotracheal tubes should cause less tracheal trauma and therefore fewer immediate sequelae. An explanation may be that tracheal tube cuffs produce tracheal–mucosal membrane or ciliary damage in direct relation to the cuff–tracheal wall contact area, which is known to be largest when low-pressure, high-volume cuffs are used (Loeser et al., 1976). Another explanation may be that bulkier and larger low-pressure tubes produce more damage to upper airway structures on intubation or extubation. Furthermore, it has been demonstrated in a histological study that low-pressure, high-volume tube cuffs produce grooves in the mucosa because of wrinkling of the cuffs as it is inflated, unlike the situation after inflation of high-pressure, low-volume cuffs (Loeser, Hodges et al., 1978).

The correlation between tracheal surface contact area and sore throat after operation was stressed in a report demonstrating that the frequency of postoperative sore throat could be decreased significantly by the use of narrow-cuffed endotracheal tubes (Loeser, Bennett et al., 1980).

A study on anatomical conformity led to the conclusion that tubes with standard low residual volume cuffs induced fewer sequelae than did similar cuffed tubes moulded to the pharyngeal contour, possibly because of differences in mucosal contact area throughout the upper airway (Loeser, Machin et al., 1978).

That intubation trauma *per se* causes postoperative throat symptoms is further demonstrated by the fact that intubation with uncuffed tubes induced sore throat in 40% of patients (Loeser, Stanley et al., 1980). Lubrication of tracheal tubes provides no advantage in terms of reducing sore throat after operation. It was reported that lubrication with 4% lignocaine jelly containing polyethylene and propylene glycols was associated with increased complaints after operation (Loeser, Stanley et al., 1980). However, it had been shown earlier that patients might benefit from lubrication of tracheal tubes with 1% cinchocaine jelly (Winkel and Knudsen, 1971).

The fact that a mask technique is followed by sore throat is usually ascribed to the drying of mucous membranes after ventilation with dry gases and to the use of antisialagogues (Loeser et al., 1976).

The role of cuff to tracheal wall pressure in inducing sore throat is minor. Loeser, Machin and others (1978) were able to demonstrate a high frequency of sore throat after intubation with tracheal tubes with Kamen–Wilkinson foam-filled cuffs. Furthermore, it was shown that changes in intracuff volume or pressure during anaesthesia were poorly correlated with the occurrence of sore throat, as was intubation time (Loeser et al., 1976).

Nitrous oxide diffuses into cuffs of tracheal tubes, thereby increasing cuff volume and pressure (Stanley, Kawamura and Graves, 1974; Stanley, 1975; Revenäs and Lindholm, 1976; Bernhard et al., 1978). In some studies (Loeser et al., 1976; Loeser, Machin et al., 1978) cuffs were filled with air. One might believe that high-volume, low-pressure cuffs would sustain greater volume increases than low-volume, high-pressure cuffs, when filled with air and exposed to nitrous oxide, thereby causing an increased frequency of sore throat. However, it has been demonstrated that changes in cuff volume and pressure are similar in the two groups when intubation time is about 120 min (Stanley, 1975).

The minor role of cuff pressure *per se* was further reported in a study confirming that the frequency of postoperative sore throat after tracheal intubation with high residual volume, low-pressure cuffs is independent of cuff-filling with a sample of the inspired mixture of gases, room air or saline (Stanley and Loeser, 1979). Although the minor role of pressure seems to be established, it is known that cuff inflation beyond the seal point significantly increases the measured intracuff/lateral wall pressures and thereby possibly the cuff-tracheal contact area too (Wu et al., 1973).

We have confirmed that low-volume, high-pressure cuffs induced sore throat to a lesser extent than did high-volume, low-pressure cuffs, provided that intracuff volumes were maintained at the level of "just-seal" throughout anaesthesia. When intracuff pressure in the low-volume, high-pressure cuffed tubes was high and allowed to increase, this advantage disappeared.

The relative overinflation of cuff in our group C probably increased the cuff–tracheal wall contact area as was observed in the experimental part of the study. However, it is obvious that direct comparison of cuff length in the experimental model with the clinical situation can be questioned, in as much as tracheal compliance differs in the two situations. Many factors are involved in the aetiology of sore throat. To minimize the occurrence of this phenomenon after short-term intubation with cuffed tubes, it seems that the use of low-volume cuffed tubes is preferable, provided that intracuff pressures are kept as low as possible to establish the minimum seal either by serial adjustments or by use of the anaesthetic mixture when inflating the cuff.

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MAL DE GORGE APRES L'INTERVENTION: INFLUENCE DE L'INTUBATION TRACHEALE, DE LA PRESSION DANS LE BALLONNET ET DU TYPE DE BALLONNET

RESUME

Nous avons étudié 184 patients pour préciser le rôle de la pression dans le ballonnet et du type de ballonnet dans la survenue d'un mal de gorge et d'une raucité de la voix après une intervention. Les patients ont été classés dans l'un des groupes suivants: A = masque seul; B = sonde de Rüsch réutilisable sans réajustement intermittent du volume du ballonnet; C = sonde de Rüsch réutilisable sans reajustement du volume du ballonnet; D = sonde Portex jetable à filet bleu avec réajustement intermittent du volume du ballonnet; E = sonde de Shiley basse pression jetable avec réajustement intermittent du volume du ballonnet. Le pro-

toxyde d'azote a été utilisé comme adjuvant de l'anesthésie chez tous les patients. Des symptomes modérés ou sévères ont été rapportés chez 30–33% des patients des groupes C, D et E, alors que dans le groupe B, ces séquelles n'étaient retrouvées que chez 10% des patients ($P < 0{,}025$). C'est dans le groupe A que les séquelles sont survenues les plus rarement ($P < 0{,}025$). Les femmes avaient plus de risque de développer un mal de gorge aprés intubation que les hommes ($P < 0{,}01$). On évoque l'existence d'une influence possible de différences de surface de contact entre le ballonnet et la trachée.

HALSENTZÜNDUNG NACH OPERATION: DER EINFLUẞ DER TRACHEALEN INTUBATION, DES DRUCKES IN DER BLOCKERMANSCHETTE UND DER ART DER MANSCHETTE

ZUSAMMENFASSUNG

Es wurden 184 Patienten untersucht, um den Einfluß des Druckes im Cuff und die Art des Cuffs bei postoperativer Heiserkeit und Halsentzündung festzustellen. Die Patienten wurden in folgende Gruppen eingeteilt: A = nur mit Maske; B = mehrmals verwendbarer Rüsch-Tubus mit intermittierender Cuff-Volumen-Einstellung; C = mehrmals verwendbarer Rüsch-Tubus ohne Cuff-Volumen-Einstellung; D = Einmal-Portex-Blue-Line-Tubus mit intermittierender Cuff-Volumen-Einstellung; E = Einmal-Shiley-Niederdruck-Tubus mit intermittierender Cuff-Volumen-Einstellung. Bei allen Narkosen wurde Lachgas verwendet. Mäßiggradige oder ernsthafte Beschwerden wurden bei 30 bis 33% der Patienten in den Gruppe C, D und E festgestellt, während in der Gruppe B nur bei 10% der Patienten Beschwerden als Folge der Intubation auftraten ($P < 0{,}025$). Alle diese Befunde kamen in der Gruppe A mit geringerer Häufigkeit als in den anderen Gruppen vor ($P < 0{,}025$). Es zeigte sich, daß Frauen mehr als Männer nach der Intubation an einer Halsentzündung litten. Eine mögliche Beziehung zwischen unterschiedlicher Kontaktfläche des Cuffs und der Trachealwand wird postuliert.

IRRITACION DE GARGANTA DESPUES DE LA OPERACION QUIRURJICA: INFLUENCIA DE LA INTUBACION TRAQUEAL, DE LA PRESION INTRACOLLARIN Y DEL TIPO DE COLLARIN

SUMARIO

Se estudiaron ciento cuatro pacientes con el fin de elucidar la contribución de la presión intracollarín y del tipo de collarín, a la aparición de irritaciones de garganta y ronquera después de la operación. A los pacientes se les asignó a uno de los siguientes grupos: A: solo máscara; B: tubo Rüsch reutilizable con ajuste intermitente del volumen del collarín; C: tubo Rüsch reutilizabla con ajuste del volumne del collarín; D: tubo Portex Blue Line no reutilizable con ajuste del volumen del collarín; E: tubo Shiley no reutilizable y de baja presión con ajuste intermitente del volumen del collarín. El óxido nitroso fue un componente de la anestesia administrada a todos los pacientes. Se registraron síntomas moderados o graves en el 30–33% de los pacientes pertenecientes a los grupos C, D y E, en contraste con los del grupo B en los que estas secuelas sólo se apreciaron en el 10% de los pacientes ($P < 0{,}025$). Todas las secuelas aparecieron con menos frecuencia en el grupo A que en ninguno de los otros grupos ($P < 0{,}025$). Las mujeres fueron más propensas a desarrollar irritación de garganta después de la intubación de lo que lo fueron lo hombres ($P < 0{,}01$). Se postula una posible relación entre las diferencia del contacto entre la tráquea y el collarín.

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A STUDY OF GLYCOPYRROLATE AND ATROPINE IN THE SUPPRESSION OF THE OCULOCARDIAC REFLEX DURING STRABISMUS SURGERY IN CHILDREN

J. E. HUNSLEY, G. H. BUSH AND C. J. JONES

SUMMARY

Glycopyrrolate 5 and 7.5 μg kg^{-1} and atropine 10 and 15 μg kg^{-1} were studied in 80 paediatric patients to assess more fully the dose of glycopyrrolate required for adequate prevention of the oculocardiac reflex. A dose-related improvement in protection from this reflex was seen with both drugs, but neither drug prevented reductions in heart rate in every patient. A nodal rhythm was the most common arrhythmia observed with both drugs. In the doses used, no adverse effects were noted and no further anticholinergic treatment was required during muscle traction. Higher doses may be associated with an increase in side-effects with more pronounced dryness of the mouth and tachycardia and, with atropine, a greater likelihood of the production of the "central anticholinergic syndrome".

Glycopyrrolate (Robinul) is a quaternary ammonium anticholinergic compound which has been evaluated in premedication (Mirakhur et al., 1978; Mirakhur, Dundee and Connolly, 1979; Lavis, Lunn and Rosen, 1980), and in combination with an anticholinesterase for the reversal of non-depolarizing muscle relaxants (Wong et al., 1974; Black et al., 1980; Cozanitis et al., 1980) in both adult and paediatric patients. However, minimal data exist on its efficacy in preventing the oculocardiac reflex in children, and the optimal dosage for its use in this situation has not been fully evaluated (Venugopal, Asrani and Winnie, 1977; Meyers and Tomeldan, 1979).

The objectives of this study were to investigate the efficacy and dose–effect relationship for glycopyrrolate in the suppression of the oculocardiac reflex, and to compare glycopyrrolate with the reported equivalent doses of atropine (Mirakhur, Dundee and Jones, 1978; Lavis, Lunn and Rosen, 1980).

PATIENTS AND METHODS

Eighty healthy children of either sex, undergoing elective surgery for correction of strabismus were studied. They had no pre-existing cardiovascular disease and were not receiving anticholinergic drugs. The ages of the patients were 1–12 yr; weight range 10–45 kg. Concurrent medications excluding anticholinergics were continued.

A standardized anaesthetic technique was used. Premedication was with trimeprazine 1.5 mg kg^{-1} (maximum dose 30 mg) given orally 3 h before surgery and morphine sulphate 0.25 mg kg^{-1} (maximum dose 10 mg) i.m. 1 h before surgery. Anaesthesia was induced with thiopentone 4 mg kg^{-1} i.v. and relaxation for endotracheal intubation was provided by tubocurarine 0.8 mg kg^{-1}. Anaesthesia was maintained by manual intermittent positive pressure ventilation of the lungs using nitrous oxide and oxygen (2:1 ratio) with a Jackson–Rees modification of the Ayres T-piece. The fresh gas flow was adjusted to maintain Pa_{CO_2} at about 4.7 kPa (Watt and Nightingale, 1980). At the end of surgery, muscular relaxation was reversed using i.v. neostigmine 0.08 mg kg^{-1} and atropine 0.02 mg kg^{-1}.

Glycopyrrolate and atropine were used in concentrations of 0.2 mg ml^{-1} and 0.4 mg ml^{-1} respectively. The drugs were administered i.v. in a randomized manner 5 min before induction of anaesthesia. Each patient received one dose of either drug in a large or a small dose (glycopyrrolate 5 or 7.5 μg kg^{-1} or atropine 10 or 15 μg kg^{-1}), from coded ampoules supplied by A. H. Robins Co. Ltd. The investigator was aware if a large or small dose of the test drug was being given, but was unaware of the identity of the drug. Four groups of 20 patients were studied.

The effects of the drugs on heart rate and rhythm

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were monitored with intermittent recording of the electrocardiograph (e.c.g.), taken at the times shown in table I. The e.c.g. recordings were analysed by calculating the mean heart rate over 20 consecutive complexes, at each of the times mentioned in table I. The slowest heart rate during maximum traction of the rectus muscle was assessed by measuring the longest individual R–R wave interval. Any arrhythmias were noted from the time the e.c.g. was attached to the patient until after traction on the eye muscles had ceased.

TABLE I. *Times at which e.c.g. recordings were taken*

(a)	0.5 min before administration of test drug
(b)	1 min following test drug
(c)	2 min following test drug
(d)	3 min following test drug
(e)	4 min following test drug
(f)	5 min following test drug
(g)	1 min before induction of anaesthesia
(h)	1 min following induction of anaesthesia
(i)	1 min before endotracheal intubation
(j)	1 min following endotracheal intubation
(k)	1 min before and continuously during traction of the rectus muscles

Changes in heart rate after eye muscle traction were compared statistically between the groups by non-paired *t* test and Mann–Whitney analysis. Heart rates within the groups were analysed with a paired *t* test. The frequency of arrhythmias in each group were compared using the Chi-square test.

RESULTS

The ages of the patients in this study ranged from 1 to 12 yr, and their weights ranged from 10 to 37 kg. A summary of the mean ages and weights in each group is shown in table II.

Changes in heart rate after administration of the test drug

Table III shows the mean heart rates for each group from before administration of the test drug, and at the times shown in table I, until after endotracheal intubation. The mean heart rates of each group before administration of the test drug were similar. The changes in heart rate shown in table III are illustrated in figure 1 as percentage increases in heart rate. Groups 1, 2 and 3 show an increase in mean heart rate of less than 25% 5 min after the test drug, whereas the mean heart rate in group 4 increased by more than 34%. The increase in heart rate was statistically significant in all of the four groups ($P < 0.001$). However, the difference between the groups was not statistically significant. The onset of action of atropine in both doses was faster than that of glycopyrrolate.

TABLE II. *Age and weight distributions*

	Age (yr)		Weight (kg)	
	Mean ± SEM	Range	Mean ± SEM	Range
Group 1 Glycopyrrolate 5 μg kg^{-1}	6.85 ± 0.65	3–12	22.90 ± 1.71	14–37
Group 2 Glycopyrrolate 7.5 μg kg^{-1}	4.95 ± 0.61	1–10	18.95 ± 1.42	10–29
Group 3 Atropine 10 μg kg^{-1}	5.10 ± 0.52	2–10	20.20 ± 1.40	12–35
Group 4 Atropine 15 μg kg^{-1}	6.55 ± 0.76	2–12	20.25 ± 1.44	12–35

Changes in heart rate after traction on the rectus muscle

The number of tractions on the lateral and medial rectus muscles is shown for each group in table IV. Figure 2 illustrates the mean percentage decrease in heart rate after muscle traction, compared with the heart rate 1 min before muscle traction. It can be seen that traction on the medial rectus had a greater effect on the heart rate than traction on the lateral rectus. Using the data for both muscles, group 1 slowed by 33.3% compared with 30.7% slowing in group 3. Similarly, groups 2 and 4 slowed by 23.8%

TABLE III. *Mean heart rates at the various times stated in table I*

	Mean heart rates (beat min^{-1} ± SEM)			
Times	Group 1 (glycopyrrolate 5 μg kg^{-1})	Group 2 (glycopyrrolate 7.5 μg kg^{-1})	Group 3 (atropine 10 μg kg^{-1})	Group 4 (atropine 15 μg kg^{-1})
(a)	112 ± 7.20	113 ± 5.49	117 ± 6.08	113 ± 6.05
(b)	120 ± 7.03	122 ± 6.46	132 ± 7.35	137 ± 5.82
(c)	125 ± 6.35	129 ± 6.42	132 ± 7.11	141 ± 5.50
(d)	127 ± 6.18	134 ± 5.86	135 ± 7.16	143 ± 5.69
(e)	129 ± 6.28	134 ± 5.91	135 ± 7.61	144 ± 5.56
(f)	132 ± 6.07	138 ± 5.64	138 ± 7.90	143 ± 5.02
(g)	136 ± 6.25	139 ± 6.01	143 ± 6.77	148 ± 5.41
(h)	153 ± 3.94	152 ± 5.72	153 ± 5.58	156 ± 6.02
(i)	153 ± 3.94	152 ± 5.72	153 ± 5.58	156 ± 6.02
(j)	171 ± 4.08	172 ± 4.95	175 ± 3.84	171 ± 4.52

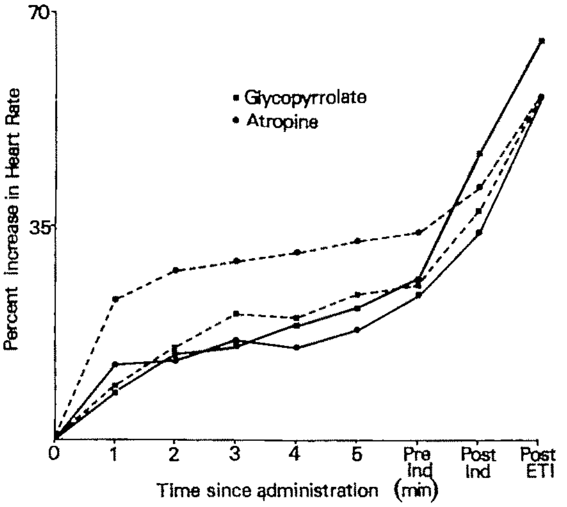

FIG. 1. Mean percentage increases in heart rate following the administration of the test drugs. Ind = induction of anaesthesia; ETI = endotracheal intubation. --- = high dose. —— = low dose.

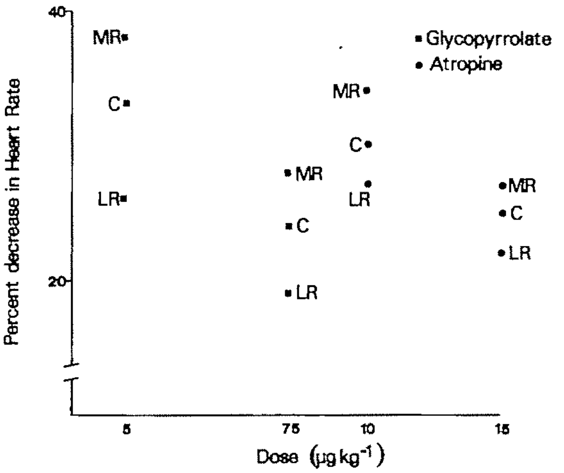

FIG. 2. Mean percentage decrease in heart rate after rectus muscle traction for each group. MR = medial rectus; LR = lateral rectus. C = combined data for both muscles.

and 25.1% respectively. Both drugs therefore showed a dose-related response for reduction in slowing of heart rate after rectus muscle traction, but the difference was not statistically significant. Figure 3 shows the range of heart rates resulting from individual muscle tractions. It can be seen that there is great individual variation in response to muscle traction within each group, no group being fully protected from marked slowing in heart rate. Figure 4 shows the percentage decreases in heart rate after muscle traction. Again, it indicates that some individuals show marked slowing of heart rate after muscle traction, whereas others are fairly well protected. Although five children had a heart rate of less than 60 beat min^{-1} at some time during the traction on the rectus muscle, at no time did any of the reductions in heart rate give cause for clinical concern, and no treatment was given. All quickly recovered spontaneously to a reasonable level without cessation of surgery.

TABLE IV. *Number of muscle tractions in each group*

	Muscle tractions		
	Medial rectus	Lateral rectus	Total
Group 1 Glycopyrrolate 5 µg kg^{-1}	19	12	31
Group 2 Glycopyrrolate 7.5 µg kg^{-1}	19	15	34
Group 3 Atropine 10 µg kg^{-1}	19	16	35
Group 4 Atropine 15 µg kg^{-1}	16	12	28

Frequency of arrhythmias before muscle traction

One patient had frequent ventricular extrasystoles before the test drug was given, which improved progressively after glycopyrrolate 5 µg kg^{-1} and disappeared before induction of anaesthesia.

A second patient had recurrent nodal rhythm before administration of the test drug, and this arrhythmia again disappeared after giving glycopyrrolate 5 µg kg^{-1}.

A third patient developed nodal rhythm 3 min after glycopyrrolate 5 µg kg^{-1}. After induction of anaesthesia it resolved, but reappeared after traction of the rectus muscle.

A fourth patient developed ventricular extrasystoles 4 min after glycopyrrolate 7.5 µg kg^{-1}. It again disappeared after induction of anaesthesia, but did not recur after muscle traction.

A fifth patient developed ventricular extrasystoles after atropine 10 µg kg^{-1} but they disappeared after endotracheal intubation. They recurred after traction on the rectus muscle.

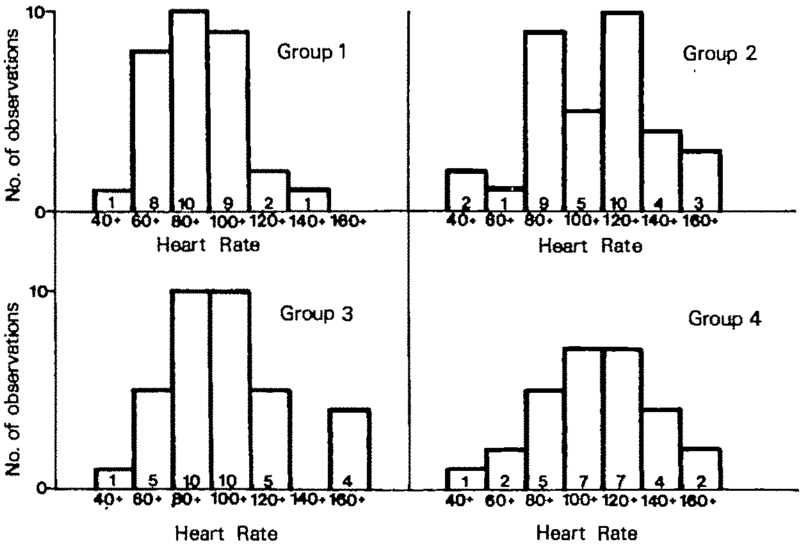

FIG. 3. Slowest heart rate (beat min^{-1}) developed after each rectus muscle traction.

Arrhythmias after muscle traction

Table V shows the frequency of arrhythmias during rectus muscle traction. The main arrhythmia seen was nodal rhythm with only a few instances of ventricular extrasystoles. In groups 1 and 3, 13 and eight patients respectively developed an arrhythmia compared with only three arrhythmias in group 2 and none in group 4. The differences between the high and low doses with both drugs were statistically significant ($P<0.01$) using the Chi-squared analysis.

All arrhythmias resolved spontaneously without treatment and at no time caused a clinically obvious deterioration in cardiac function.

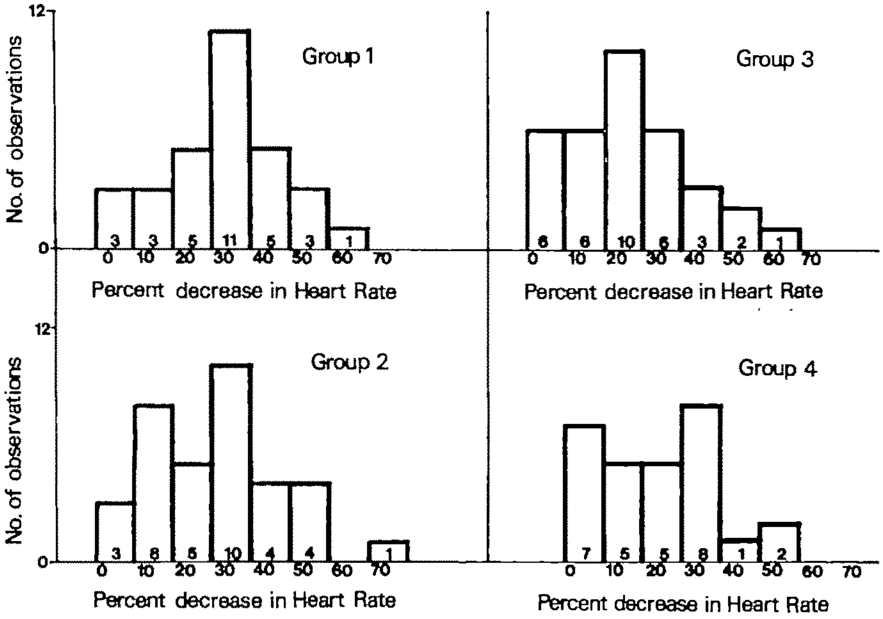

FIG. 4. Percentage decrease in heart rate after each rectus muscle traction.

TABLE V. *Frequency of arrhythmias*

	Patients with arrhythmias		
	Total	Nodal rhythm	Ventricular extrasystoles
Group 1 Glycopyrrolate $5\,\mu g\,kg^{-1}$	13	13	1
Group 2 Glycopyrrolate $7.5\,\mu g\,kg^{-1}$	3	3	0
Group 3 Atropine $10\,\mu g\,kg^{-1}$	8	7	2
Group 4 Atropine $15\,\mu g\,kg^{-1}$	0	0	0

Miscellaneous observations

The antisialagogue properties of both drugs provided satisfactory conditions at intubation and during recovery from anaesthesia, even at the lower doses.

It is interesting to note that three patients in group 4 and one patient in group 3 became markedly drowsy within a few seconds of receiving the i.v. dose of test drug. None of the patients receiving glycopyrrolate was affected in this manner.

DISCUSSION

This study indicates that, in children, the increase in heart rate produced by atropine is greater than that from glycopyrrolate at these doses. This finding differs from the observation of Mirakhur, Jones and Dundee (1981), in adults, that glycopyrrolate in a dose of $10\,\mu g\,kg^{-1}$ had a slightly greater effect on heart rate than atropine $20\,\mu g\,kg^{-1}$. Using larger doses, they found that the effects of the drugs on heart rate were reversed, with atropine having a greater effect, as in this study. Our study shows that the onset of action and peak effect of atropine is quicker than with glycopyrrolate as previously shown in adults using larger doses.

The study by Lavis, Lunn and Rosen (1980) showed that, in children, glycopyrrolate administered i.v. before induction of anaesthesia caused less tachycardia than atropine after 1 min, but because of the cardiovascular changes produced during induction of anaesthesia and endotracheal intubation the subsequent changes in heart rate were distorted and the differing speeds on onset of action were not clearly seen.

In this study, after rectus muscle traction it was found that no group was fully protected from reduction in heart rate. There was a dose-related response in groups 2 and 4 when compared with groups 1 and 3 with regard to the mean decrease in heart rate, but little difference existed between the two drugs. A most striking observation was the great individual variation within the groups of the protection offered by the drugs. Some patients showed very little or no decrease in heart rate, whilst others had marked reductions in heart rate (see figs 3, 4).

Three patients developed an arrhythmia soon after the test drug was given, one after glycopyrrolate $5\,\mu g\,kg^{-1}$, one after glycopyrrolate $7.5\,\mu g\,kg^{-1}$ and one after atropine $10\,\mu g\,kg^{-1}$. This represents a frequency of 3.75% of the total patients in the trial. The study by Lavis, Lunn and Rosen (1980), reported a frequency not markedly different from this study. Here five out of 60 children developed either a nodal rhythm or ventricular extrasystoles, three occurring after glycopyrrolate and two after atropine.

In this study, after muscle traction, the frequency of arrhythmias in the glycopyrrolate groups was more than in the atropine groups, but this was not statistically significant. There was, however, a dose–response effect, producing a statistically significant ($P < 0.01$) lessening in the frequency of arrhythmias with the higher doses of both drugs. The study by Meyers and Tomeldan (1979), consisting mainly of children, reported complete protection from bradycardia (a decrease in heart rate greater than 30%) and arrhythmias during rectus muscle traction after i.v. administration of atropine $20\,\mu g\,kg^{-1}$ and glycopyrrolate $10\,\mu g\,kg^{-1}$.

Therefore it would appear that atropine $15\,\mu g\,kg^{-1}$ and glycopyrrolate $7.5\,\mu g\,kg^{-1}$ i.v. given 5 min before induction of anaesthesia are not sufficient to protect completely against the oculocardiac reflex in children. If higher doses are used to prevent the undesirable arrhythmias and reductions in heart rate seen during extraocular surgery, then side-effects such as excessively dry mouth and tachycardia must be accepted. This study suggests that atropine can cross the blood–brain barrier, whereas glycopyrrolate is less likely to do so (Proakis and Harris, 1978). Thus, in higher doses necessary to prevent the oculocardiac reflex, the "central anticholinergic syndrome" may be more frequently encountered with atropine.

ACKNOWLEDGEMENTS

We are grateful to A. H. Robins Co. Ltd for supplying the drugs used in this study, and also for the secretarial and statistical facilities provided. We would like to thank Dr D. A. Nightingale for his help and encouragement. Mr Clements and Mr Patterson kindly gave permission for their patients to be included in this study. Lastly, the help of Mr Fred Waddington and all the nursing staff in theatre and on the wards is much appreciated.

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ETUDE DU GLYCOPYRROLATE ET DE L'ATROPINE DANS LA SUPPRESSION DU REFLEXE OCULOCARDIAQUE AU COURS DE LA CHIRURGIE DU STRABISME CHEZ L'ENFANT

RESUME

Le glycopyrrolate 5 et 7,5 μg kg^{-1} et l'atropine, 10 et 15 μg kg^{-1}, ont été étudiés chez 80 enfants pour préciser davantage la dose de glycopyrrolate nécessaire à une prévention correcte du reflexe oculo-cardiaque. Une protection dose-dépendante vis à vis de ce réflexe a été observée avec les deux agents, mais aucun des deux ne prévenait les bradycardies chez tous les patients. Le trouble du rythme le plus fréquent, observé avec l'un et l'autre produit, est le rythme nodal. Aux doses utilisées, on n'a observé aucun effet délétère et l'on n'a pas eu besoin d'autre traitement anticholinergique au cours des tractions sur les muscles. Des doses plus élevées peuvent entraîner des effets secondaires plus importants avec une sécheresse marquée de la bouche et une tachycardie, et avec l'atropine, un plus grand risque d'apparition du "syndrome anticholinergique central".

UNTERSUCHUNG ÜBER DIE UNTERDRÜCKUNG DES OKULO-KARDIALEN REFLEXES DURCH GLYCOPYRROLATE UND ATROPIN WÄHREND STRABISMUS-OPERATIONEN BEI KINDERN

ZUSAMMENFASSUNG

Glycopyrrolate 5 und 7,5 μg kg^{-1} und Atropin 10 und 15 mg kg^{-1} wurden bei 80 pädiatrischen Patienten untersucht. Zweck der Studie war es, genau festzustellen, welche Dosis von Glycopyrrolate zur Verhinderung des okulo-kardialen Reflexes erforderlich ist. Eine dosisabhängige Zunahme mit Schutz des Reflexes wurde bei beiden Medikamenten gesehen, doch war keines der beiden Mittel in der Lage, bei allen Patienten die Abnahme der Herzfrequenz zu verhindern. Die häufigste Rhythmusstörung bei beiden Mitteln war der Knotenrhythmus. Mit der benützten Dosierung wurden keine unerwarteten Wirkungen beobachtet und es war auch keine weitere anticholinergische Behandlung während des Ziehens an den Augenmuskeln erforderlich. Höhere Dosierungen können mit einer Zunahme von Nebenwirkungen wie stärkere Trockenheit des Mundes und Tachykardie einhergehen. Außerdem kann es bei Atropie mit höherer Wahrscheinlichkeit zum Auftreten des "zentralen anticholinergischen Syndromes" kommen.

UN ESTUDIO DEL GLICOPIRROLATO Y DE LA ATROPINA EN LA SUPRESION DEL REFLEJO OCULOCARDIACO DURANTE LA OPERACION QUIRURJICA DE ESTRASBISMO EN NIÑOS

SUMARIO

Se estudió en 80 pacientes pediátricos el efecto de 5 μg kg^{-1} y de 7,5 μg kg^{-1} de glicopirrolato y de 10 μg kg^{-1} y 15 μg kg^{-1} de atropina con el fin de evaluar con más exactitud la dosis de glicopirrolato necesaria para prevenir adecuadamente el reflejo oculocardiaco. Se observó que ambas drogas producían una mejora, en función de la dosis, de la protección contra este reflejo, pero ninguna de ellas impidió las reducciones del ritmo cardiaco en cada uno de los pacientes. La arritmia más común que se observó como consecuencia de la droga fue un ritmo nodal. No se apreciaron efectos secundarios negativos como consecuencia de la droga, ni fue necesario tratamiento anticolinérgico adicional durante la tensión muscular. Las dosis más elevadas pueden venir asociadas con un incremento de los efectos secundarios, una mayor sequedad de la boca y con taquicardia; con la atropina hay una probabilidad mayor de que se produzca el "síndrome anticolinérgico central".

Br. J. Anaesth. (1982), 54, 465

CHANGES IN COLLOID OSMOTIC PRESSURE AND PLASMA ALBUMIN CONCENTRATION ASSOCIATED WITH EXTRACORPOREAL CIRCULATION

R. SANCHEZ DE LÉON, J. L. PATERSON AND M. K. SYKES

SUMMARY

Colloid osmotic pressure (COP), plasma albumin concentration, haematocrit, and blood-gas tensions were measured in 16 patients undergoing open-heart surgery with cardiopulmonary bypass. The use of crystalloid priming and cardioplegia solutions resulted in a 60% decrease in COP, a 48% decrease in plasma albumin concentration and a 35% decrease in haematocrit. These measurements had returned to pre-perfusion values 6 h after the end of surgery. The alveolar–arterial P_{O_2} difference increased significantly after by-pass and returned to pre-perfusion values within the same time scale. Right-to-left shunt increased from 7.9 to 10.3% 30 min after the end of by-pass. It is concluded that, in the absence of an increase in left atrial pressure, marked decreases in COP can be tolerated without the occurrence of pulmonary oedema.

In the early days of open-heart surgery the priming volumes of the extracorporeal circuits were large and the primes consisted mainly of whole blood. The subsequent introduction of bubble and membrane oxygenators with small priming volumes permitted crystalloid or colloid primes to be used, thereby minimizing the hazards associated with the use of homologous blood.

Studies of respiratory function after perfusion with a rotating-disc oxygenator primed with two-thirds whole blood and one-third lactated Ringer's solution showed that there was no significant increase in alveolar–arterial oxygen tension difference ($P_{A_{O_2}} - P_{a_{O_2}}$) or total venous admixture in the period immediately after bypass (Seed, Sykes and Finlay, 1970; Sykes et al., 1970). Routine blood-gas monitoring indicated also that the introduction of bubble oxygenators primed with 1–3 litre of lactated Ringer's solution had no significant effect on pulmonary function.

In recent years myocardial preservation has been achieved by the perfusion of 1–2 litre of iced cardioplegia solution into the coronary circulation. This fluid is usually allowed to drain into the perfusion circuit so that further haemodilation occurs. Patients subjected to this technique commonly display signs of widespread peripheral oedema. In addition, some patients have developed severe arterial hypoxaemia during the period after bypass despite the administration of inspired oxygen concentrations of 50–60% and mechanical ventilation with a positive end-expiratory pressure of 0.5–1.0 kPa. Although there have been no obvious signs of pulmonary oedema on the chest radiograph after surgery, and there have been no gross changes in airway resistance or total thoracic compliance, it seemed possible that the arterial hypoxaemia might have been caused by an accumulation of lung water. Since the arterial hypoxaemia had not been associated with a significant increase in left atrial pressure we decided to study the changes in colloid osmotic pressure and plasma albumin concentration associated with this technique of cardiopulmonary bypass.

PATIENTS AND METHODS

Studies were performed on 16 patients aged between 43 and 63 yr, who were being subjected to open-heart surgery with cardiopulmonary bypass. Fourteen patients were male and two female. Twelve patients underwent coronary artery vein bypass grafts, two had mitral valve replacements and two had aortic valve replacements. The duration of operation varied between 185 and 390 min and the duration of bypass between 50 and 130 min. The surface area of the patients varied between 1.55 m^2 and 2.10 m^2 (mean 1.99 m^2).

The patients were premedicated with papaveretum and hyoscine supplemented, where

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necessary, with small doses of droperidol or lorazepam. The anaesthetic consisted of thiopentone, pancuronium, phenoperidine, nitrous oxide and oxygen, the inspired oxygen concentrations being adjusted to produce an arterial $P\text{O}_2$ (Pa_{O_2}) in the range 13–20 kPa. Ventilation was controlled with an Engström 300 ventilator at frequencies of 12–14 b.p.m. Tidal volumes of 500–700 ml were required to maintain an arterial $P\text{CO}_2$ (Pa_{CO_2}) in the range of 4–5 kPa, and an end-expiratory positive pressure of 0.5 kPa was added to maintain a normal functional residual capacity (FRC) when the chest was open. Ventilation was continued during the bypass period using a mixture of oxygen 1–2 litre and air 2 litre. The lungs were hyperinflated several times at the end of bypass. Controlled ventilation was maintained for 3–18 h after operation and discontinued when the cardiovascular system was stable.

The operation was performed through a median sternotomy, the pleura being opened accidentally on one side on only one occasion. The patients were cooled to 28–30 °C during cardiopulmonary bypass with a Rygg–Kyvsgaard bubble oxygenator. The circuit was primed with 1.5–2.0 litre of lactated Ringer's solution and a small quantity of sodium bicarbonate solution. The basal flow rate was 2.4 litre m^{-2} body surface area, but this was increased by 30–40% when the haematocrit was low. Additional quantities of lactated Ringer's solution (1–2 litre) were added during bypass to maintain the circulating volume and if the haemotocrit decreased to less than 20–25%, homologous blood (stored for 1–2 days in citrate–phosphate–dextrose anticoagulant) was added to the circuit. When the oesophageal temperature had been decreased to 30 °C, 1 litre of cardioplegia solution (1 litre of lactated Ringer's containing $\text{MgCl}_2.6\text{H}_2\text{O}$ 16 mmol, KCl 16 mmol and procaine HCl 1 mmol) was injected to the coronary circulation to cool the heart to less than 10 °C. Further increments of 0.5–1.0 litre were required in nine patients. The solution drained into the left ventricular vent and coronary sinus and so mixed with the other fluid in the perfusion circuit. Urine output was measured every 30 min and frusemide administered whenever the output decreased to less than 1 ml min^{-1}.

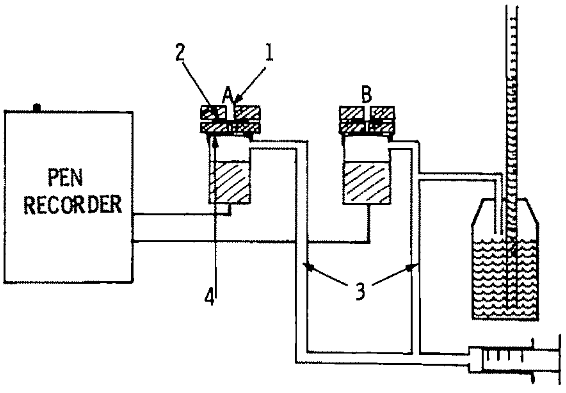

FIG. 1. Double oncometer system with pressure calibration apparatus. A, B = oncometers. 1 = well for substance under test; 2 = membrane; 3 = tubing connecting syringe and water manometer to reference side of transducer diaphragms; 4 = pressure transducer diaphragm. The space between the membrane and diaphragm was filled with saline.

The volume of blood transfused in the period after bypass and in the intensive care unit was determined by measured blood loss and right atrial pressures. Arterial pressure was maintained close to preoperative values by the use of vasodilator or inotropic drugs.

Measurements. Arterial blood-gas tensions and pH, serum potassium concentration and haematocrit were monitored throughout the procedure. Measurements of colloid osmotic pressure (COP), serum albumin concentration and haematocrit were made on blood samples drawn at the induction of anaesthesia, just before bypass, 10 min after commencing bypass and every 30 min thereafter until the end of bypass. Additional samples were taken just before the patient was returned to the Intensive Care Unit (usually 1–2 h after the end of bypass) and 3, 6 and 12 h later. The samples were centrifuged immediately and all measurements completed within a few hours of sampling.

COP was measured with a pressure transducer system which was a modification of the osmometer described by Aukland and Johnsen (1974). The unit consisted of two cylindrical metal blocks with a semipermeable membrane sandwiched between them (fig. 1). The lower block replaced the threaded dome of a standard Consolidated Dynamics differential pressure transducer (4-327-L222) and had a central channel which was filled with boiled saline (to exclude air bubbles). The membrane was sealed between the two metal blocks by means of rubber O-rings. The upper block contained a central channel with a volume of 0.3 ml. This served as a reservoir for the solution under test. When a solution with a greater osmotic pressure than saline was placed in the reservoir it created an osmotic pressure gradient across the membrane which forced the transducer diaphragm upwards. The movement of the diaphragm was detected by the strain gauge in the transducer and the signal from the transducer was then amplified and displayed on a Devices heated-stylus recorder.

The membrane chosen for these measurements was Amicon PM 10. This had a typical rejection of >98% for albumin whilst the typical maximal deionized water flow was 1–4 ml cm^{-2} min^{-1}. The membrane had a rapid response and readings quickly returned to zero when physiological saline was placed in the reservoir (fig. 2).

The zero was adjusted before each measurement when the cuvette contained saline. The gain control was also adjusted before each measurement by applying step increases in pressure of 1, 2 and 2.5 kPa to the back of the transducer diaphragm through the reference pressure inlet. This pressure was generated by injecting air into a reservoir connected both to the tranducer and to a saline manometer. This method of calibration stressed the diaphragm in the same direction as that produced by a hyperosmolar solution and confirmed that the output of the transducer was linear to within ±0.01 kPa. Hysteresis was also within these limits. Assessments of the functioning of the oncometer and on the reproducibility of the measurements were performed with a reference solution containing albumin 50 g $litre^{-1}$ and globulin 33 g $litre^{-1}$ (Sigma Laboratories), and with a second albumin solution containing 45 g $litre^{-1}$ in saline. The former solution read 3.6 (±0.1) kPa and the latter 2.4 (±0.1) kPa on our oncometers. These solutions were split into samples of 1 ml and kept in a refrigerator at −10 °C, one tube of each solution being used for reproducibility checks twice a day. All the measurements of COP were made at room temperature (23–26 °C) and the values were corrected to the patient's temperature from the equation:

$$\mathrm{COP}_{t_2} = \frac{273 + t_2}{273 + t_1} \times \mathrm{COP}_{t_1}$$

where t_1 and t_2 were the respective temperatures of the room and the patient in degrees Celsius.

No correction was made for the pH or $P\mathrm{CO}_2$ of the plasma. The sample was covered by a plastic cover during the measurement and duplicate measurements were obtained on each sample by running two oncometers in parallel. Duplicates always agreed within ±0.1 kPa throughout the study.

Albumin concentrations were measured in duplicate by the Bromocresol green method (Sigma Chemical Co. P.O. Box 14508, St Louis, Missouri

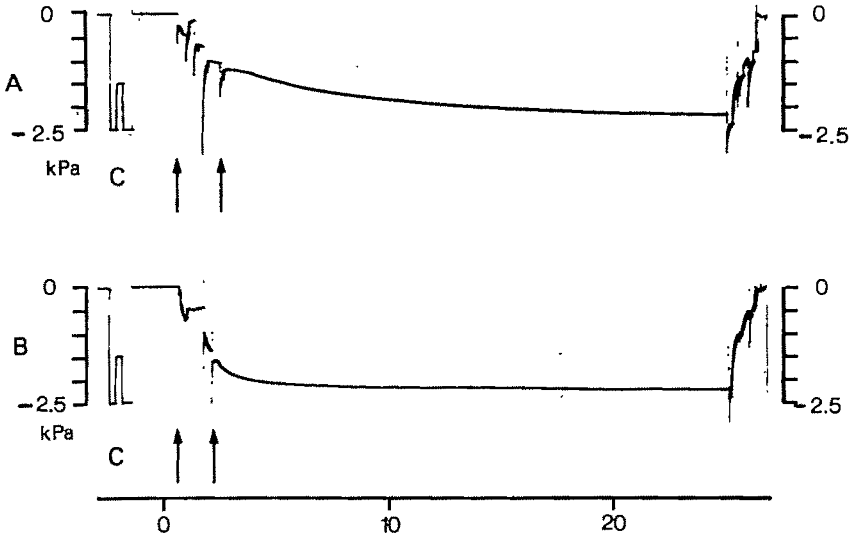

FIG. 2. Recordings from oncometers A and B. C = pressure calibration: −1.5 and −2.5 kPa. Three to four aliquots of sample were inserted into the well on each oncometer between the arrows. Oncometer B (with a new membrane) responded more quickly than oncometer A, but both reached the same final value (−2.2 kPa) after 20–25 min. Both wells were then flushed with saline to check that there had been no zero drift.

63178, U.S.A.) (Doumas, Watson and Biggs, 1971) and haematocrit was determined by the standard method using a microcentrifuge. Inspired oxygen tension (PI_{O_2}) was measured by an oxygen electrode or paramagnetic analyser and blood-gas tensions and pH by a Radiometer ABL 1 automated system which was checked daily by tonometered blood samples (Selman and Tait, 1976). In six patients in this group and 11 other patients measurements of total venous admixture were made using arterial and pulmonary artery samples obtained by direct puncture at operation. These were analysed for oxygen content (Ca_{O_2} and $C\bar{v}_{O_2}$) by the Lex-O_2-Con analyser (Selman, White and Tait, 1975) and the values used to provide the arteriovenous oxygen content difference in the modified shunt equation:

$$\frac{\dot{Q}s}{\dot{Q}t} = \frac{(Cc'_{O_2} - Ca_{O_2})}{(Cc'_{O_2} - Ca_{O_2}) + (Ca_{O_2} - C\bar{v}_{O_2})}$$

The difference between the end-pulmonary capillary and arterial oxygen contents (Cc'_{O_2} and Ca_{O_2}) in both numerator and denominator was calculated from the ideal alveolar PO_2 (PA_{O_2}), the arterial PO_2 and the arterial pH. These values were used to derive end-pulmonary capillary and arterial saturations by reference to the standard dissociation curve (Severinghaus, 1966). Content was calculated from the haemoglobin, saturation and PO_2 assuming that each gram of haemoglobin combined with 1.34 ml of oxygen. Ideal alveolar PO_2 was calculated from the simplified equation:

$$PA_{O_2} = PI_{O_2} - \frac{Pa_{CO_2}}{0.8}$$

The statistical analysis was performed using an analysis of variance and Student's paired *t* tests.

RESULTS

The average volume of Ringer's lactate solution administered during bypass was 2.56 litre (range 2.0–3.8 litre) and the average volume of cardioplegia solution was 1.5 litre. The total quantity of crystalloid administered during bypass therefore ranged from 2.5–5.8 litre. One patient required 2 units of blood during bypass because of low haematocrit. An average of 2.52 litre (range 1.5–5.5 litre) of blood was infused during operation and a further 2.27 litre (range 0.99–2.36 litre) was given in the 24 h after operation. Crystalloid administration in the latter period averaged 0.60 litre. Urine output averaged 1.07 litre (range 0.67–1.85 litre) during and after bypass and 1.42 litre (range 0.2–2.82 litre) in the 24 h after operation.

The patients remained in the intensive care unit for 20–28 h and were mechanically ventilated for 3–18 h (mean 14 h) after operation. There was no gross radiological evidence of pulmonary oedema in the x-rays taken in the supine position immediately after operation. Four patients required dopamine after operation. Two patients died after the period of study, one from intractible arterial hypertension and another from cerebral embolic problems.

There were no significant differences between the induction and pre-bypass COP measurements. There was a significant decrease in COP ($P < 0.05$) from a mean of 2.69 kPa before bypass to 1.08 kPa 10 min after instituting bypass (table I and fig. 3). There was little change during bypass. In the 13

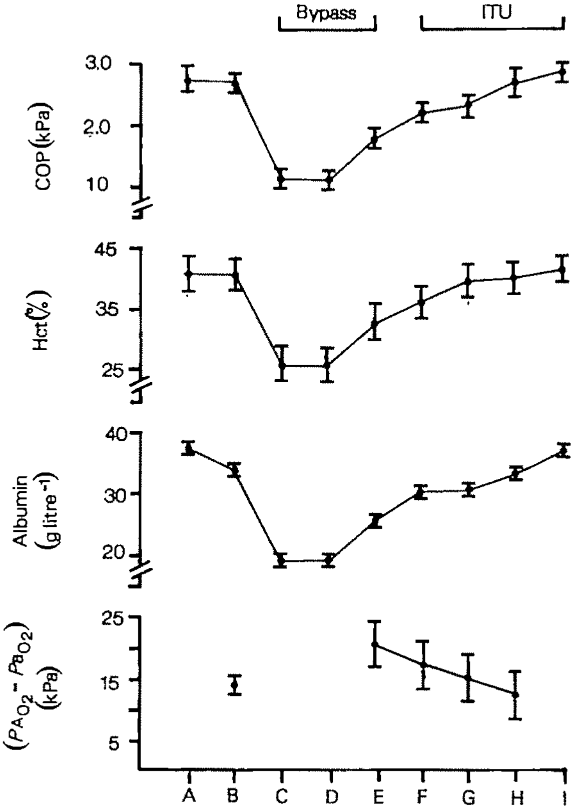

FIG. 3. Colloid osmotic pressure (COP), haematocrit (Hct), plasma albumin concentrations and alveolar–arterial PO_2 differences ($PA_{O_2} - Pa_{O_2}$). Values are means ± SEM. A = at induction; B = before bypass; C = 10 min after starting bypass; D = 30 min later, E = end of bypass; F = end of operation; G, H and I = 3, 6 and 12 h after end of operation

TABLE I. *Changes in colloid osmotic pressure, plasma albumin concentration and haematocrit during operation and the period after operation (mean ± SEM). A = induction; B = before bypass; C = 10 min after starting bypass; D = 30 min later; E = end of bypass; F = end of operation; G, H, and I = 3, 6, and 12 h after end of operation*

	A	B	C	D	E	F	G	H	I
Colloid osmotic pressure (kPa)	2.73 ±0.25	2.69 ±0.15	1.08 ±0.16	1.19 ±0.15	1.75 ±0.17	2.20 ±0.19	2.44 ±0.20	2.68 ±0.30	2.87 ±0.15
Haematocrit (%)	40.4 ±3.9	40.1 ±4.0	26.3 ±3.8	26.4 ±3.6	33.1 ±3.4	36.6 ±3.4	39.1 ±4.0	39.6 ±3.7	41.5 ±2.5
Albumin (g litre^{-1})	37.0 ±1.0	34.0 ±1.2	18.0 ±1.1	19.0 ±1.0	26.0 ±1.1	31.0 ±1.2	31.0 ±1.3	34.0 ±1.2	37.0 ±1.2
$(PA_{O_2} - Pa_{O_2})$ (kPa)	— —	14.1 ±2.8	— —	— —	20.3 ±4.1	17.1 ±4.7	15.8 ±4.9	12.5 ±4.7	— —

patients studied 10, 40 and 70 min after commencing bypass the means were 1.11, 1.13, and 1.21 kPa respectively. In the four patients in whom samples were obtained after 100 min on bypass the mean was 1.04 kPa compared with 1.25 kPa at the start of bypass. However, for the group as a whole the COP had increased to 1.75 kPa at the end of bypass and had reached pre-bypass values by the 6th hour after operation. The pattern of change of albumin concentration was similar. Haematocrit decreased from a mean of 40.4% before bypass to 26.3% on bypass but had returned to pre-bypass values by the 3rd hour following operation.

The alveolar–arterial $P\text{O}_2$ difference $(PA_{O_2} - Pa_{O_2})$ increased from a mean of 14.1 kPa before bypass to 20.3 ± 4.1 kPa about 30 min after the end of bypass ($P < 0.05$). Mean $(PA_{O_2} - Pa_{O_2})$ was 17.1 kPA at the end of operation, 15.8 kPa 3 h later and had returned to 12.5 kPa 6 h after the end of operation. In the 17 patients in whom intrapulmonary shunt was measured before and 30 min after bypass (table II) there was increase from a mean of 7.9 ± 3.2% to 10.3 ± 4.5% ($P < 0.05$). The majority of the patients showed only a small increase in shunt, but in one patient the shunt increased from 9 to 23%. This patient required inspired oxygen concentrations of more than 50% and the application of a positive end-expiratory pressure of 5–10 cm H_2O for a period of 10 h after bypass.

DISCUSSION

These studies have shown that cardiopulmonary bypass with a crystalloid prime and additional cardioplegia solution decreased COP to 40%, albumin concentration to 53% and haematocrit to 65% of the pre-perfusion values. The addition of further crystalloid solution during bypass tended to maintain those values throughout bypass periods of up to 100 min, but after bypass the values returned towards normal. In the majority of patients there was an increase in $(PA_{O_2} - Pa_{O_2})$ and only a small increase in intrapulmonary shunt in the period immediately after bypass, but one patient developed a marked increase in shunt for a period of 10 h after operation.

Ladegaard-Pedersen (1967) studied some of the factors which affect the measurement of COP in patients. He found that there was a daily variation of ± 10.5% in patients who were confined to bed, and he also showed that the COP of such patients was 0.4–0.5 kPa less than when they were ambulant. Our initial values were usually taken a few minutes

TABLE II. *Arterial and mixed venous blood-gas tensions, haemoglobin (Hb) concentration, oxygen contents and percentage shunt before and 30 min after bypass in 17 patients*

	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	$(PA_{O_2} - Pa_{O_2})$ (kPa)	$P\bar{v}_{O_2}$ (kPa)	$P\bar{v}_{CO_2}$ (kPa)	Hb (g dl^{-1})	Ca_{O_2} (mmol litre^{-1})	$C\bar{v}_{O_2}$ (mmol litre^{-1})	$(Ca_{O_2} - C\bar{v}_{O_2})$ (mmol litre^{-1})	Shunt (%)
Before										
Mean	25.35	4.38	16.38	5.67	5.04	13.64	8.43	6.43	2.00	7.90
SD	±6.04	±0.81	±5.87	±0.65	±0.83	±1.33	±0.83	±0.78	±0.43	±3.23
After										
Mean	24.89	4.95	16.41	6.23	5.92	11.13	6.96	5.35	1.61	10.3
SD	±5.84	±1.17	±5.77	±0.65	±1.56	±1.37	±0.93	±0.80	±0.34	±5.4

after the induction of anaesthesia and the pre-perfusion values about 1 h later, after the administration of 100–200 ml of Ringer's lactate solution. Both means were smaller than the means of 3.9, 3.2 and 4.0 kPa reported by Losowsky, Alltree and Atkinson (1962), Ladegaard-Pedersen (1967) and English, Digerness and Kirklin (1971). However, our values were close to those reported by Marty and colleagues (1973). Since the latter authors used a membrane similar to ours it seems likely that the disparities were a result of differing membrane characteristics.

English, Digerness and Kirklin (1971) reported that COP decreased from a mean of 4.0 kPa before bypass to a mean of 2.5 kPa during bypass. Perfusion was carried out with a rotating-disc oxygenator and a prime of 4 units of acid–citrate–dextrose blood, 750 ml of 5% dextrose in 0.45% sodium chloride and 1250 ml of balanced salt solution (Normosol). The initial haematocrit of their perfusate was 30% and alternate units of blood and salt solution were given during the remainder of the bypass period. They observed that COP increased to a mean of 2.7 kPa 3 h after the end of bypass and then remained unchanged for 24 h. However, they noted that in the single patient with a bypass time of 180 min both the COP and total protein concentration remained less than that observed in the other patients during the period after bypass.

Further studies on patients subjected to cardiopulmonary bypass were reported by Marty and co-workers (1973). These authors investigated two primes. One contained 150 ml of 5% dextrose solution and 500 ml of acid–citrate–dextrose whole blood with a further 2500–3000 ml of balanced salt solution (Normosol) and 75 g of salt-poor albumin. Variable amounts of ACD blood (500–400 ml) were added during bypass. With the first prime mean oncotic pressure decreased by 41% from 2.7 kPa to 1.6 kPa and with the second it decreased by 42% from 3.1 kPa to 1.8 kPa. By the 4th hour after bypass COP was more than 90% of the pre-bypass value in both groups. Thus the intraoperative administration of an average of 155 g of salt-poor albumin did not significantly affect the average increase in oncotic pressure after operation.

English, Digerness and Kirklin (1971) found that total protein concentration decreased from 75 g litre^{-1} to 48 g litre^{-1} whilst Marty and colleagues (1973) found a similar decrease from a mean of 63 g litre^{-1} to 40 g litre^{-1}. Although the pattern of change of COP is similar to the pattern of change in albumin concentration, the relationship between the two is not necessarily linear and in chronic situations it is not always possible to predict one from the other (Losowsky, Alltree and Atkinson, 1962). However, in our own studies a close correlation was observed between COP and both haematocrit and plasma albumin concentration (fig. 4). Thus, it appears that haemodilution with crystalloid solutions decreases the plasma protein concentration and COP and so may alter the Starling equilibrium across the capillary wall.

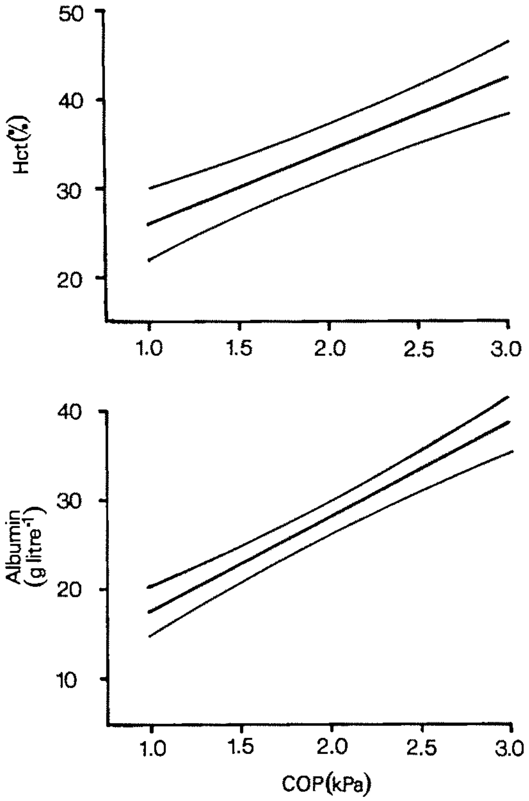

FIG. 4. Correlation (regression lines with 95% tolerance limits) of haematocrit (Hct) and plasma albumin concentration against colloid osmotic pressure (COP).

Although most of the patients studied had obvious peripheral oedema with swollen eyelids, distension of the tissues of the face, neck and limbs and pitting oedema over the sacrum, there was remarkably little evidence of alveolar or interstitial oedema. $(P\mathrm{A}_{\mathrm{O}_2} - P\mathrm{a}_{\mathrm{O}_2})$ increased after bypass but returned to pre-bypass values during the ensuing 6 h. An increase in $(P\mathrm{A}_{\mathrm{O}_2} - P\mathrm{a}_{\mathrm{O}_2})$ during ventilation with 50% oxygen could be the result of an increase in intrapulmonary shunt, but could also be caused by a decrease in mixed venous $P\text{O}_2$, an alteration in haemoglobin concentration or a shift of the oxygen dissociation curve. In order to clarify the significance of the increase in ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) we made measurements of intrapulmonary shunt using direct measurements of arterial and mixed venous oxygen contents. Only one of the 17 patients so studied showed an increase in shunt of more than 4%. This patient had received 2 litre of cardioplegia solution and developed a shunt of 23% 30 min after bypass. The impairment in gas exchange persisted for 10 h after the end of the operation but responded to treatment with 50% oxygen and a positive end-expiratory pressure of 5–10 cm H_2O. Although this patient showed no clinical or radiological evidence of pulmonary oedema, it is believed that the increased shunt was caused by terminal airway closure resulting from interstitial oedema.

Muir and colleagues (1975) infused 2 litre of normal saline into normal seated subjects at a rate of 100 ml min^{-1} and found that these subjects had an increase in closing volume without any change in their lung compliance or flow–volume characteristics. Furthermore, in the two subjects in whom closing volume exceeded the functional residual capacity after infusion there was also a decrease in arterial $P\text{O}_2$. Narrowing of the small terminal airways has little effect on airway resistance since the total cross sectional area of these airways is large and the velocity of airflow small. Terminal airway narrowing or closure may therefore occur without obvious changes in airway resistance (Hogg et al., 1972; Hauge, Bø and Waaler, 1975). Thus there is experimental evidence to support the suggestion that the decrease in colloid osmotic pressure might have increased fluid transudation into the interstitial space and so caused arterial hypoxaemia by narrowing terminal airways and decreasing ventilation in dependent lung zones. This concept is further supported by the observation that the application of PEEP has rapidly corrected the arterial hypoxaemia in most of the patients who have developed a low arterial $P\text{O}_2$ after bypass.

The mechanisms which protect the lung from pulmonary oedema when COP is decreased have been studied in baboons subjected to acute isovolaemic decreases in plasma oncotic pressure by plasmapheresis (Zarins et al., 1978). In these experiments plasma COP was decreased by 76% (from 2.6 to 0.6 kPa) whilst pulmonary capillary pressure was maintained at a normal value. This resulted in a seven-fold increase in pulmonary lymph flow and, although there was marked peripheral oedema, there was no increase in the wet lung/dry lung weight ratio. The increased lymph flow in these experiments was accompanied by a reduction in the lymph albumin concentration and by a decrease in lymph COP though the lymph/plasma COP ratio was unchanged. Thus the decrease in plasma COP resulted in an increase in lymph flow but appeared to produce little change in the filtration pressure gradient. It is of interest that, in pulmonary oedema resulting from increased hydrostatic pressure, Staub (1974) found a decrease in the lymph/plasma COP ratio which would have further protected against pulmonary oedema formation. It is possible that a similar change in the lymph/plasma COP ratio would have been observed in the experiments of Zarins and co-workers (1978) if the measurements had been prolonged further.

An additional factor which must be considered is tissue pressure. In most tissues the interstitial space is easily distended and can therefore accommodate relatively large volumes of fluid with little change in pressure (Guyton and Lindsey, 1959). In the lung the interstitial space around the capillaries is bounded by tight epithelial junctions and a collagen framework so that a relatively small increase in interstitial fluid volume probably leads to a significant increase in interstitial pressure (Fung, 1974; Guyton, Taylor and Granger, 1975). This in turn would tend to decrease fluid transfer from the capillary to the interstitial space.

Two other factors probably minimized the occurrence of pulmonary oedema in these patients. First, the lung was not perfused during the period of maximal haemodilution. During the period immediately after bypass COP rapidly increased so that the period during which the lung was exposed to a significant decrease in COP was limited. Second, a positive end-expiratory pressure was maintained during anaesthesia.

The mechanism by which PEEP improves oxygen transfer in patients with pulmonary oedema is still not known. Although Barach, Martin and Eckman (1938) and Ashbaugh and colleagues (1969) originally postulated that an increase in alveolar pressure might alter the pressure gradients across the alveolar capillary membrane and so decrease the transudation of fluid into the interstitial space, many investigators have found that the application of PEEP results in no change or even an increase in lung water (Wagner et al., 1961; Mellins et al., 1969; Caldini, Leith and Brennan, 1975; Demling, Staub and Edmunds, 1975; Thornton et al., 1975). Therefore, it has been suggested that most of the improvement is a result of the opening of collapsed lung units as a result of an increase in FRC (Kumar et al., 1970) or of a decrease in pulmonary blood flow secondary to a decrease in venous return to the heart. Although recent work using the isolated perfused rabbit lung preparation suggests that an increase in alveolar pressure can reduce fluid filtration under certain conditions, the interplay of many factors makes interpretation of the experimental results very difficult (Bø, Hauge and Nicolaysen, 1977; Smith-Erichsen and Bø, 1979).

The present studies confirm that extreme haemodilution can result in a marked decrease in plasma albumin concentration and in plasma COP. In the majority of patients this may lead to marked peripheral oedema without evidence of gross pulmonary oedema providing left atrial pressure is maintained at normal values. However, in a few patients the decrease in COP is associated with an impairment in oxygen transfer within the lung. This may be caused by interstitial pulmonary oedema and terminal airway closure. Therefore, it is important to monitor the blood-gas tensions frequently in the period after bypass. Diuretics should be given if urine flow is inadequate and any decreases in arterial P_{O_2} to less than normal values should be treated by increasing the inspired P_{O_2} and applying a positive end-expiratory pressure.

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MODIFICATIONS DE LA PRESSION COLLOIDO-OSMOTIQUE ET DE LA CONCENTRATION PLASMATIQUE D'ALBUMINE INDUITES PAR LA CIRCULATION EXTRACORPORELLE

RESUME

Nous avons mesuré la pression colloïdo-osmotique (PCO), la concentration plasmatique d'albumine, l'hématocrite et les gaz du sang chez 16 patients subissant un acte de chirurgie à coeur ouvert sous circulation extracorporelle (CEC). L'utilisation de solutions cristalloïdes de commencement et de cardioplégie a entraîné une diminution de 60% de la PCO, une diminution de 48% de la concentration plasmatique d'albumine et une diminution de 35% de l'hématocrite. Ces paramètres avaient retrouvé leur valeur de départ 6 h aprés la fin de l'acte chirurgical, de façon significative après la CEC et trouvait sa valeur de départ dans le même délai. Le shunt droit gauche passait de 7,9% à 10,3%, 30 min après la fin de la CEC. Nous en concluons que, en l'absence d'augmentation de la pression dans l'oreillette gauche, des diminutions importantes de la PCO peuvent être tolérées sans que l'on voit apparaître d'oedème pulmonaire.

VERÄNDERUNGEN VON KOLLOID-OSMOTISCHEM DRUCK UND PLASMA-ALBUMIN BEI EXTRAKORPORALEM KREISLAUF

ZUSAMMENFASSUNG

Bei 16 Patienten mit offener Herzoperation und kardiopulmonalem Bypass wurden kolloid-osmotischer Druck (KOD), Plasma-Albumin-Konzentration, Hämatokrit und Blutgaswerte gemessen. Die Verwendung von Elektrolyt-Lösungen und Infusionslösungen mit Kardioplegika führte in 60% der Fälle zu einer Abnahme des KOD, in 48% zu einer Abnahme der Plasma-Albumin-Konzentration und in 35% zu einer Abnahme des Hämatokrits. Diese Werte kehrten 6 Stunden nach Operationsende auf die Höhe der Ausgangswerte vor Beginn der Infusionstherapie zurück. Die alveolär–arterielle P_{O_2}-Differenz stieg nach dem Bypass signifikant an und kehrte innerhalb derselben Zeit zu den Ausgangswerten zurück. Der Rechts-Links-Shunt nachm 30 min nach Ende des Bypasses von 7,9 auf 10,3% zu. Wir schließen daraus, daß solange der Druck im linken Vorhof nicht ansteigt, eine deutliche Abnahme des KOD toleriert wird, ohne daß es zu einem Lungenödem kommt.

CAMBIOS DE LA PRESION OSMOTICA COLOIDAL Y DE LA CONCENTRACION DE ALBUMINA EN EL PLASMA ASOCIADOS CON LA CIRCULACION EXTRACORPOREA

SUMARIO

Se midieron la presión osmótica coloidal (POC), la concentración de albúmina en el plasma y las tensiones hemotocritas y gaseosas en 16 pacientes sometidos a intervención quirúrjica a pecho abierto con desviación cardiopulmonar. El uso de imprimación cristaloidea y de soluciones cardioplégicas tuvieron como resultado una disminución del 60% en la POC, del 48% en la concentración de albúmina en el plasma y de un 35% en la tensión hematocrita. Las mediciones efectuadas volvieron a adquirir los valores previos a la perfusión seis horas después de la intervención quirúrjica. La diferencia de P_{O_2} alveolo–arterial aumentaron de forma significativa después de la desviación y volvieron a adquirir los valores previso a la perfusión dentro de la misma escala de tiempos. El transvase de derecha a izquierda aumentó desde el 7,9 al 10,3% a los 30 minutos después de terminada la desviación. La conclusión es que, si no existe un incremento de la presión auricular izquierda, pueden tolerarse incrementos notables de la POC sin que tenga lugar edema pulmonar.

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CORRESPONDENCE

PREOPERATIVE BUPRENORPHINE DOES NOT PREVENT MYOCLONIA SEEN AFTER ETOMIDATE

Sir,—During the development of a total i.v. anaesthesia technique based on a combined infusion of etomidate and subanaesthetic doses of ketamine, we found that one disadvantage of this combination is the myoclonia associated with etomidate (Kay and Rolly, 1977). Benzodiazepines and fentanyl reduce the frequency and severity (Holdcroft et al., 1976; Lees et al., 1981).

We tested buprenorphine 0.2 mg sublingually as a premedicant before etomidate–ketamine in a parallel study of 14 patients undergoing surgery for inguinal hernia or varicose veins in an outpatient surgical unit. We found that this dose of buprenorphine did not prevent myoclonia and we did not consider a larger dose justifiable in outpatients because of postoperative sedation.

However, we found that preoperative sublingual buprenorphine gave good preoperative sedation, and reduced the requirements for analgesic drugs in the period immediately after operation.

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I.V. SUXAMETHONIUM TEST

Sir,—Our use of suxamethonium 5 mg as described by Baraka (1978) in conscious subjects led to unexpected observations: during occlusion the fingers could be moved freely (no neuromuscular blockade); several seconds after release of the tourniquet they became immovable and generalized neuromuscular blockade required artificial ventilation for 6 min; immobility of the fingers persisted for several minutes after the return of full muscle activity elsewhere in the body (Schreiber and Plötz, 1980).

In an attempt to explain this, suxamethonium 1.5–5 mg diluted in volumes ranging from 2.5 to 40 ml was administered to anaesthetized patients while neuromuscular transmission was recorded simultaneously (adductor pollicis twitch method) (Plötz, Schreiber and Braun, 1981). During ischaemia, a twitch depression of varying degree (in some cases missing) was observed; about 30 s after release of the tourniquet a significant increase in twitch depression began. In three of eight simultaneous control studies of the other hand twitch depression commenced at the same time, although the effects were less extensive than on the test side. From these findings it was deduced that the number of suxamethonium molecules required for maximal depression reached the specific receptors not during occlusion but only systemically when the tourniquet was released. The extent of regional and systemic effects may be determined by individual sensitivity to suxamethonium. Torda and Klonymus (1967) observed a temporary increase in the neuromuscular blockade lasting 30–60 s immediately after tourniquet release in some patients, but was unable to explain the phenomenon. Baraka (1978) observed a mild ptosis, apnoea commenced in the cited case and in another patient (La Cour, Juul-Jensen and Reske-Nielsen, 1973). Plasmacholinesterase studies (table I) revealed a hereditary heterozygote status which might be responsible for the sensitivity. This genotype occurs in one in 480 individuals (Lehmann and Liddell, 1969) or even more frequently (Viby-Mogensen and Hanel, 1978) and responds unexpectedly to suxamethonium.

The occurrence of unforeseeable neuromuscular effects including apnoea, constitutes a contraindication to the use of the i.v. regional suxamethonium test in conscious patients.

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TABLE I. *Plasmacholinesterase activity and genotype* ($E_1^u E_2^a$) *after unexpected hypersensitivity to suxamethonium (investigations carried out by Drs Viby-Mogensen (Copenhagen) and Doenicke (Munich). *Repeated studies*

	Cholinesterase activity (u. litre^{-1})	Dibucaine number*	Fluoride number	Chloride number	Scoline number	Urea number
Observed value	653	66–71	46	21	72	58
Normal range	677–1560	78–86	55–65	1–22	89–95	41–52

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ADVERSE REACTION TO EXTRADURAL BUPRENORPHINE

Sir,—Many reports have demonstrated the efficacy of extradural morphine, especially in pain associated with cancer.

Buprenorphine is a new analgesic with agonist and antagonist effects (Leading Article, 1978; Kay, 1978, 1980; McQuay et al., 1980); no respiratory depression nor euphoria have been reported, but nausea and vomiting are described after i.v. and i.m. injection (Leading Article, 1978; Jasinski, Pevnick and Griffith, 1978; Kay, 1978, 1980; McQuay et al., 1980). We used buprenorphine extradurally, because two patients developed tolerance to extradural morphine. This phenomenon has been observed by Zenz and colleagues (1981).

Two women with terminal cancer were treated with extradural morphine and developed tolerance, so that morphine 12–15 mg twice daily was necessary to obtain complete analgesia.

Twelve hour after the last extradural morphine injection, buprenorphine 0.3 mg in 0.9% saline 10 ml was injected to the extradural space. Exactly 2 h later both patients developed signs of shock: pale and cold skin, low arterial pressure (90/60 mm Hg) and an average heart rate of 110 beat min^{-1}. The patients remained in this condition for nearly 2–3 h, whereafter the symptoms disappeared spontaneously. No treatment (including i.v. naloxone) was successful. The pain was then treated with extradural morphine, but only morphine 6–8 mg twice daily was necessary to secure complete pain relief.

The changed morphine sensitivity and the lack of effect of naloxone were presumably caused by the agonist/antagonist effect of buprenorphine. The injection of buprenorphine was given 12 h after the last extradural morphine, so an interaction between buprenorphine and morphine may be excluded.

We conclude that extradural buprenorphine should not be used because of the described side-effects, and also because the neurotoxic effect of buprenorphine is for the time being unknown.

F. R. CHRISTENSEN
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Frederiksborg, Denmark

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Sir,—We are glad that Dr Selwyn Crawford (1981) agrees with our "staircase pattern" expansion of the neonatal lung (Rosen et al., 1981), but question whether his "educated cheek" could generate the pattern as accurately as our apparatus.

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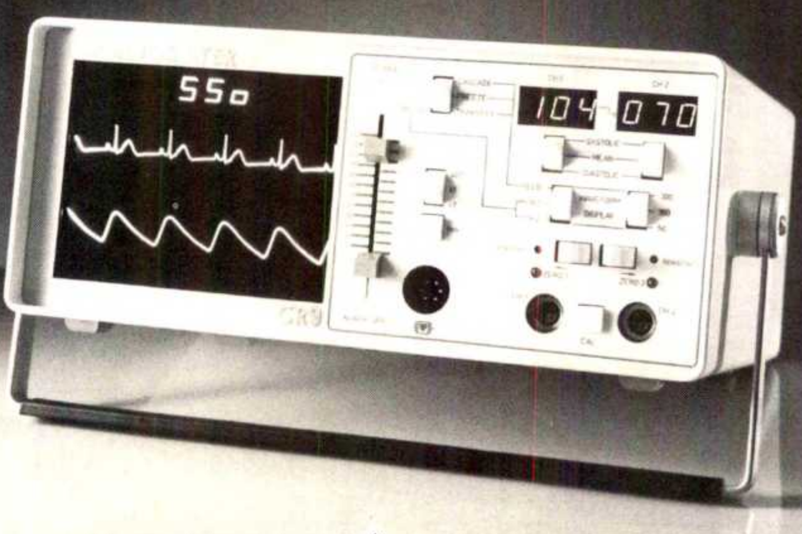

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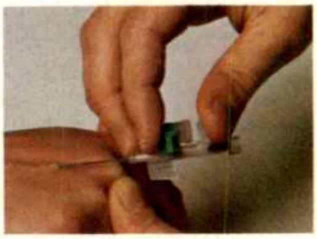

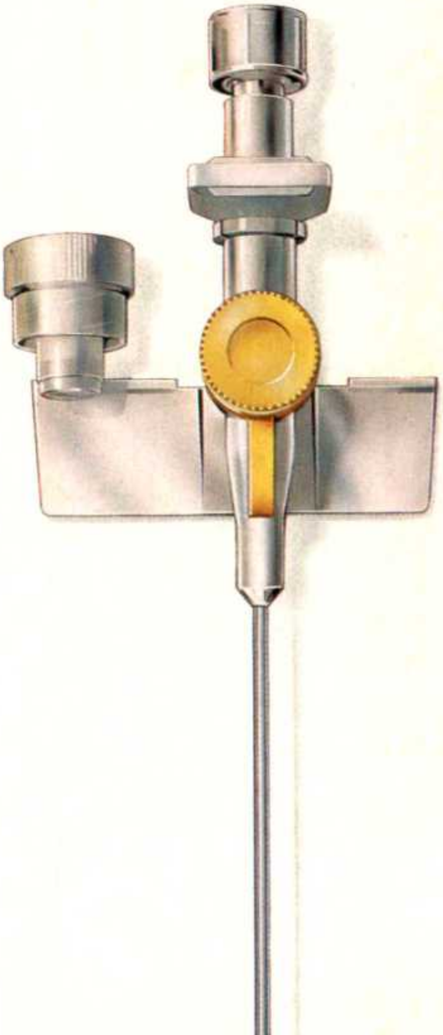

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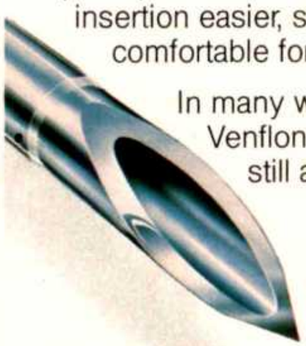

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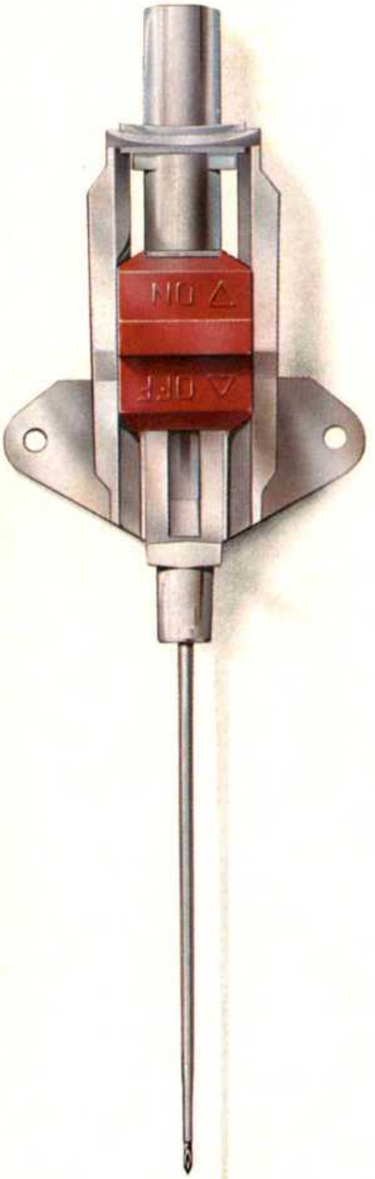

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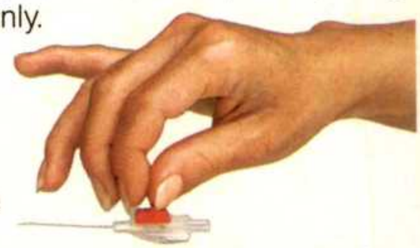

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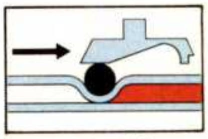

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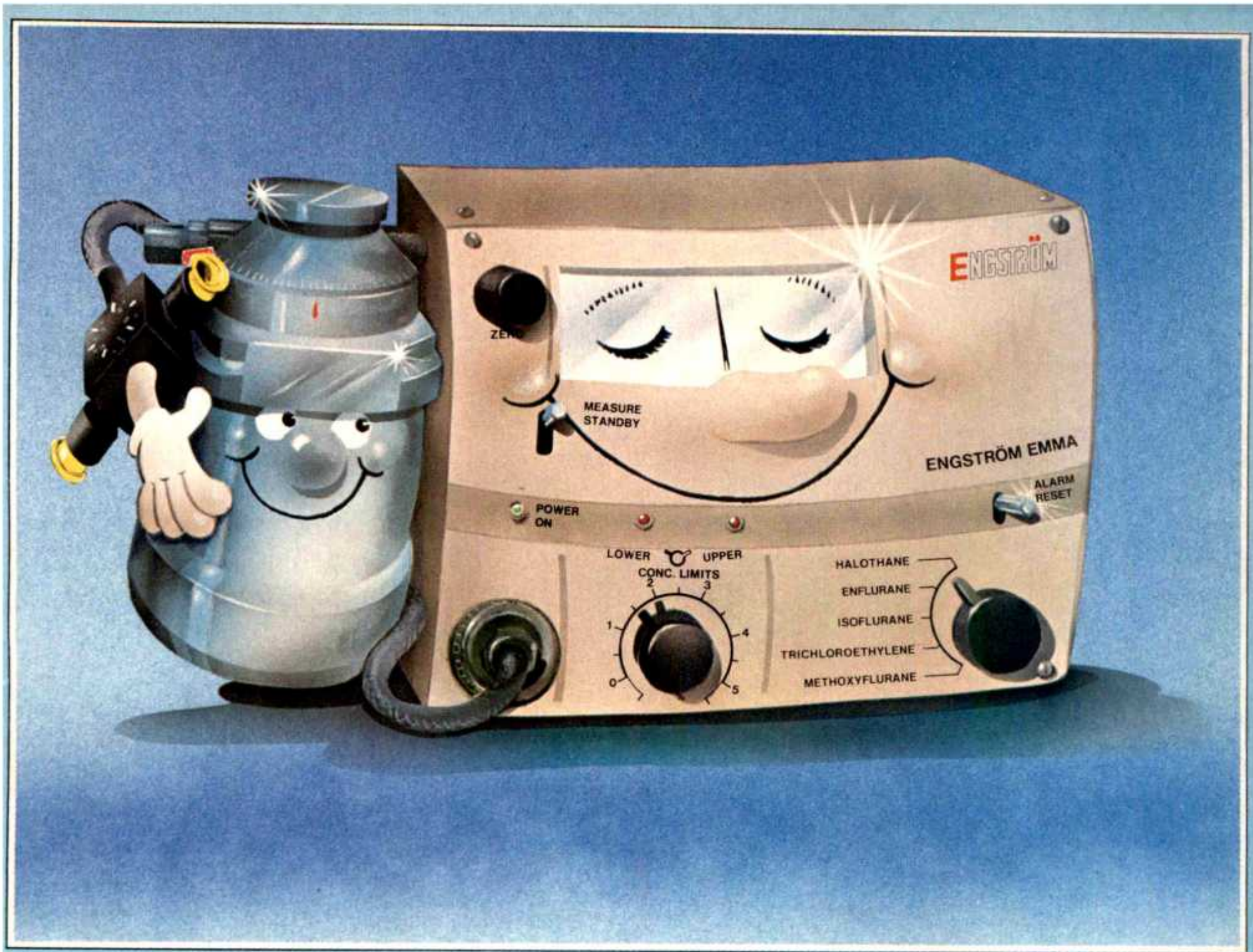

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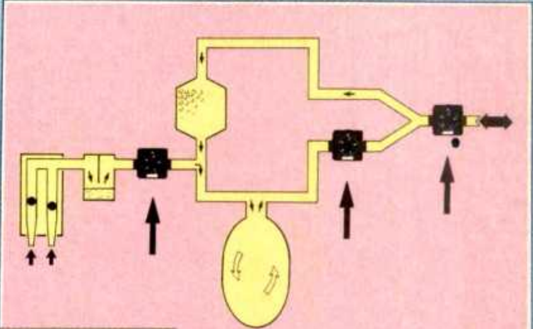

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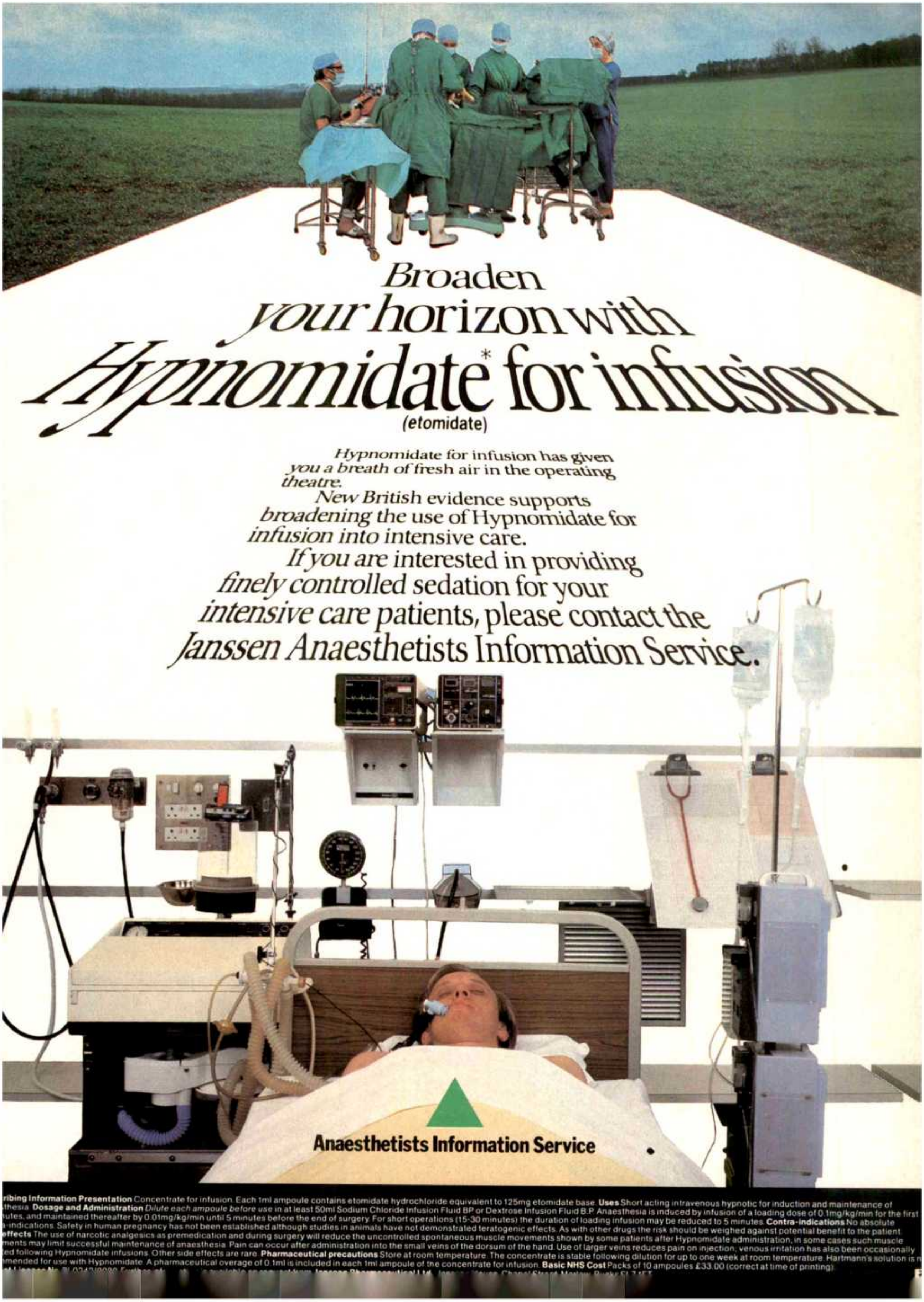

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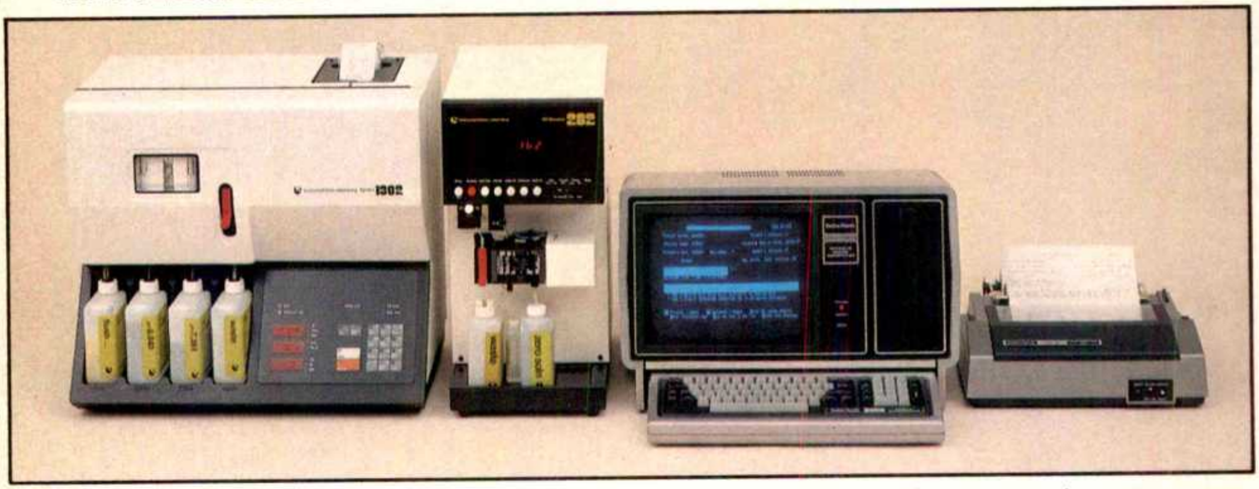

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 54, No. 5 MAY 1982

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EDITORIAL

ANAESTHETIC MORBIDITY AND MORTALITY

While learning from one's own mistakes is salutary, learning from others' mistakes is less painful and nearly as effective. Thus the enquiry into anaesthetic deaths instituted by the Association of Anaesthetists, and the Confidential Enquiry into Maternal Deaths, have yielded, or are likely to yield, valuable information from which improvements in patient care may follow. Both enquiries have relied heavily on honest and detailed reports received from the clinicians concerned and confidentiality has been of paramount importance.

Any failure in confidentiality can have serious legal consequences. Doctors associated with mishaps in clinical practice are exhorted to remain silent by their defence societies and no proper investigation can be undertaken outside a court of law. Even there the total truth is seldom arrived at.

The result of this situation is that vital information and appropriate warnings are either delayed or never forthcoming. The recent case of paraplegia following an extradural injection given to relieve labour pain, which eventually led to an award of £400 000 against a health authority is an example of this. To decide the issue of responsibility between the anaesthetist (represented by a defence society) and the midwife who gave the top-up (represented by the health authority) took 2½ years and still the clinical details are unknown to the great majority of practitioners. All the evidence from the media is that a gross error was made, but what was it?

Is there any procedure by which reports can be made by the appropriate clinicians in such cases which would be secure from legal consequences? It is unreasonable to suppose that the medical profession could be granted a degree of privilege in regard to reports made to official enquiries held by hospital authorities, but is the public interest best served by the present situation?

Perhaps the Association of Anaesthetists could organize a confidential and anonymous system whereby clinical catastrophes with an educational message could be reported. This could be along the lines of the "Yellow Card" reporting to the Committee of Safety of Medicines, but ensuring confidentiality. At the local level, is there no way in which an impartial enquiry can be held without the evidence being made available for legal proceedings? Most hospitals hold informal morbidity and mortality meetings and cases are discussed quite fully and without prejudice (in the legal sense). These meetings might provide the input to a larger enquiry leading to publication (without the revealing the sources) of the more interesting cases.

Each hospital group should generate at least a handful of incidents with an educational message for other anaesthetists. These cases would not only relate to patients who died or suffered some morbidity, but would also include "near misses".

The defence societies publish a list of cases annually, but these only concern those patients who have raised legal action against doctors. Nevertheless, the reports are avidly read by most anaesthetists and a more comprehensive report would attract considerable interest and, we would hope, make us all more aware of the pitfalls awaiting us in clinical practice.

D. B. Scott

Br. J. Anaesth. (1982), 54, 479

ADVERSE EFFECTS OF EXTRADURAL AND INTRATHECAL OPIATES: REPORT OF A NATIONWIDE SURVEY IN SWEDEN

L. L. GUSTAFSSON, B. SCHILDT AND K. JACOBSEN

SUMMARY

The Swedish Society of Anaesthetists conducted a nationwide retrospective survey of clinical experience with extradural and intrathecal opiates. Special interest was focused on the frequency and type of ventilatory depression. The questionnaire was answered by 84 of 93 departments (90%). Up to May 1981 extradural morphine had been given to approximately 6000–9150 patients, extradural pethidine to 220–450 and intrathecal morphine to 90–150 patients. Ventilatory depression requiring treatment with naloxone was reported in 23 patients treated with extradural morphine (0.25–0.40%) and in six given intrathecal morphine (4–7%). In 22 patients the administration of extradural morphine was considered as a major contributory factor for the occurrence of ventilatory depression. Only two of these 22 patients experienced ventilatory depression later than 6 h after the last dose of opiates (s.c., i.m., i.v. or extradural). Patients aged 70 yr or more, those receiving thoracic extradural puncture and those with reduced ventilatory capacity seemed to be overrepresented.

In 1979 it was demonstrated that small doses of morphine given intrathecally and extradurally produced long-lasting relief of chronic and postoperative pain in man (Bahar et al., 1979; Wang, Nauss and Thomas, 1979). The practice of this promising technique to achieve selective spinal analgesia has been hampered by the lack of controlled clinical studies (Editorial, 1980) and by reports of adverse reactions (Editorial, 1980; Reiz and Westberg, 1980; Yaksh, 1981). Pruritus and urinary retention are frequent side-effects (Reiz and Westberg, 1980; Samii, Chauvin and Viars, 1981).

An alarmingly high frequency of late respiratory depression after intrathecal administration (Davies, Tolhurst-Cleaver and James, 1980; Gjessing and Tomlin, 1981) and occasionally after extradural morphine (Boas, 1980; Christensen, 1980; Reiz and Westberg, 1980; Gustafsson, Feychting and Klingstedt, 1981) has been published.

The Swedish Society of Anaesthetists contacted the departments of anaesthesia in Sweden about the use and safety of extradural and intrathecal opiates for pain relief in clinical practice. The other aim was to estimate the frequency and elucidate the presentation of ventilatory depression after administration of extradural opiates to help in identifying patients with an increased risk for this side-effect.

MATERIALS AND METHODS

A questionnaire was sent to the head physicians of the 93 departments of anaesthesia in Sweden requesting them to report if they had used extradural or intrathecal opiates up to April 30, 1981. If so, they were asked about:

Use of extradural opiates

(a) Year and month when the department used extradural opiates for the first time.
(b) If the method was still in use, they were requested to report the indications for intra- and postoperative treatment of pain and for treatment of pain in obstetric, cancer or trauma patients.
(c) Type and amount of opiates and solutions administered extradurally.
(d) The number of patients treated with extradural morphine, pethidine or any other opiates up to April 30, 1981. If exact figures could not be given, approximate data were requested: 1–10, 11–25, 26–50, 51–100, 101–200, 201–500, 501–1000 or more than 1000 patients.

L. L. GUSTAFSSON, M.D.; K. JACOBSEN, Department of Clinical Pharmacology, Karolinska Institute, Huddinge University Hospital, S-141 86 Huddinge, Sweden. B. SCHILDT, M.D., Department of Anaesthesia, Linköping University Hospital, S-581 85 Linköping, Sweden.
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Adverse reactions to extradural morphine

We asked about the number of patients who had experienced ventilatory depression requiring naloxone, severe pruritus, neurological sequelae, urinary retention or other adverse reactions.

The reported cases of ventilatory depression were followed up by direct contact with the reporting physicians. Special interest was focused on type of operation and anaesthesia and amount of opiates administered during the periods before, during and after operation. Such data and the use of other drugs, were recorded from anaesthetic and postoperative charts.

The patients were classified into three groups: patients given extradural morphine (i) within 1 h after anaesthesia, (ii) 1 h or later after anaesthesia and (iii) patients with cancer or trauma.

Use of intrathecal opiates

Information of the same type as was requested under the previous two headings was asked for. However, the reported cases of ventilatory depression were not followed up by direct contact with the reporting physicians.

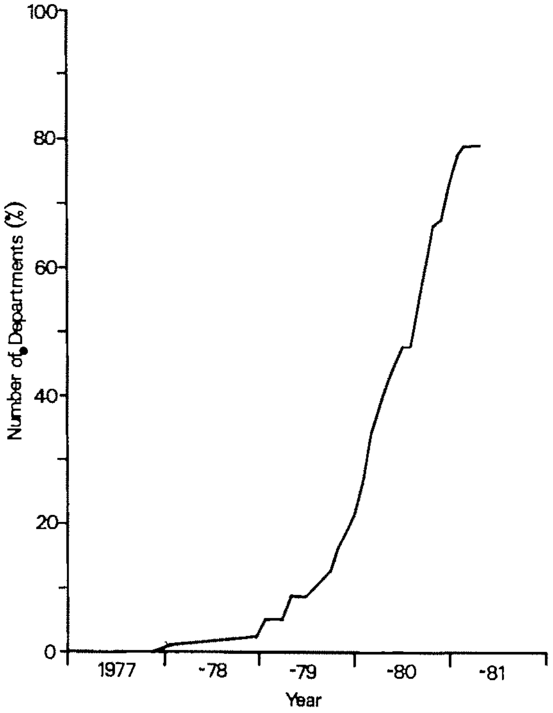

FIG. 1. The cumulative number of departments of anaesthesia in Sweden ($n = 84$) where extradural opiates were administered from 1977 to May 1981.

RESULTS

The requested information was obtained from 84 of the 93 departments (90%). Extradural opiates had been used in 67 departments and intrathecal in 10.

Use of extradural opiates

The percentage of the 84 departments that had used extradural opiates increased from less than 10% in June 1979 to more than 70% at the end of 1980 (fig. 1). This technique was still in use in 64 of 67 departments.

Between 6000 and 9150 patients were treated with extradural morphine, 220–450 with pethidine and none with other opiates. The stated standard dose of morphine for postoperative patients receiving the drug via a lumbar catheter was 2 mg in 17 departments and 4 mg in 37. At the thoracic level 2 mg was used in 17 and 4 mg in 14 hospitals.

Indications for using extradural opiates were received from 63 departments. Postoperative pain was widely accepted (83%), followed by trauma (64%), cancer pain (52%), intra- and postoperative pain (35%) and pain of obstetric procedures (6%).

Adverse reactions to extradural morphine

In 37 of the 67 departments where extradural morphine was used adverse reactions had been observed.

Ventilatory depression. Twenty-three instances of ventilatory depression requiring naloxone were reported from 15 departments. The administration of extradural morphine was considered as a major or contributory reason for the depression in 22 (tables I–III, unlikely for patient No. 23).

Only three of the 22 patients did not receive opiates additional to extradural morphine in the periods during or after operation (patients Nos 12, 14, 16). Ten of them were aged 70 yr or more and 10 had thoracic injections.

The majority of the cases of ventilatory depression occurred soon after administration of extradural morphine (fig. 2). Seven of 22 patients had depression later than 6 h after the last extradural dose of morphine. Depression more than 6 h after the last dose of opiate (as i.v., i.m., s.c. or extradural) was seen in only two patients (fig. 2).

TABLE I. *Patients with ventilatory depression (extradural morphine given within 1 h after anaesthesia)* (n = *10)*

Patient	Age (yr)	Level of catheter	Extradural morphine	Parenteral opiates	Clinical course	Comment
1	27	Lumbar	4 mg immediately after anaesthesia.	Neuroleptanaesthesia	Ventilatory depression within 30 min after extradural morphine. Naloxone given once.	Ventilatory depression induced by extradural morphine given early after neuroleptanaesthesia.
2	52					
3	58	L3–4	4 mg × 3 within 19 h, last dose immediately before bronchoscopy.	In low doses as pre-medication and during bronchoscopy.	Ventilatory depression 5 h after last dose of extradural morphine. Naloxone given once.	Ventilatory depression induced by concomitant use of extradural and parenteral opiates in a patient with chronic bronchitis.
4	>70	?	Probably 2 mg immediately after anaesthesia.	Probably 5 mg of morphine within 30 min after the extradural dose.	Ventilatory depression within 30 min after parenteral morphine. Naloxone given once.	Ventilatory depression induced by concomitant use of extradural and parenteral morphine in early postop. period.
5	>70					
6	>70	Th8–9	2 mg immediately after anaesthesia.	Neuroleptanaesthesia.	Ventilatory depression within 30 min after extradural morphine. Naloxone given once.	Ventilatory depression induced by extradural morphine given early after neuroleptanaesthesia.
7	>70	Th9–10				
8	75	Lumbar	Morphine 20 mg 30–60 min after anaesthesia.	Low doses of opiates as premedication and during operation.	Ventilatory depression requiring naloxone 12 h after extradural dose. After 6 h, 6–10 b.p.m.	Late ventilatory depression after a high extradural dose of morphine.
9	77	Th9–10	4 mg × 3 within 7 h, first dose 0.5 h after anaesthesia. Repeated doses on 1st and 2nd postop. day.	Low doses of opiates during total gastrectomy.	Ventilatory depression 8 h after last extradural dose. Naloxone administered twice within 1.5 h.	Late ventilatory depression after repeated doses of extradural morphine.
10	78	Th8–9	Morphine 2 mg 25 min after anaesthesia.	Neuroleptanaesthesia.	Ventilatory depression 3 h after extradural dose. Naloxone given once.	Ventilatory depression induced by extradural morphine given early after neuroleptanaesthesia.

TABLE II. *Patients with ventilatory depression (extradural morphine given 1 h or later after anaesthesia (n = 9). Patient No. 13 reported by Gustafsson, Feychting and Klingstedt (1981); No. 14 by Reiz and Westberg (1980); No. 18 by Modig and Paalzow (1981)*

Patient	Age (yr)	Level of catheter	Extradural morphine	Parenteral opiates	Clinical course	Comment
11	49	L1–2	4 mg 5 h after anaesthesia.	1.2 mg of leptanal during thoracotomy, moderate doses of opiate i.m. 2.5 and 6 h after anaesthesia.	Ventilatory depression 6.5 h after extradural morphine and 2 h after last parenteral dose of opiate. Dura perforation (L2–L3).	Ventilatory depression after concomitant use of extradural and parenteral opiates in a patient with dura perforation.
12 •	66	L3–4	4 mg × 2 within 3 h, first dose 7 h after anaesthesia.	None, except a small dose as premedication.	Ventilatory depression 3 h after last extradural dose. Naloxone given once.	Ventilatory depression 3 h after a repeated dose of extradural morphine.
13	68	Th7–8	2 mg × 3 within 1 h, first dose 2 h after anaesthesia.	Small doses of opiates during operation, morphine 10 mg s.c. 3 h after last extradural dose.	Ventilatory depression 5h after parenteral morphine. Naloxone given once.	Ventilatory depression 8 h after the first extradural dose of morphine and induced by concomitant use of extradural and parenteral morphine.
14	70	Thoracic	2 mg 2.5 and 12.5 h after anaesthesia.	Small dose of opiate as premedication.	Ventilatory depression 4 and 4.3 h after second dose. Naloxone given twice within 20 min.	Ventilatory depression after repeated small doses of extradural morphine.
15	70	Lumbar	Morphine 5 mg 1 h after anaesthesia.	A moderate dose of a parenteral opiate about 8 h after extradural dose.	Ventilatory depression about 9 h after the extradural and 1 h after a parenteral dose of opiate.	Ventilatory depression induced by concomitant use of extradural and parenteral opiates.
16	75	Lumbar	4 mg about 4 h after anaesthesia.	None except a small dose as premedication.	Ventilatory depression requiring naloxone 6 and 9 h after the dose.	Ventilatory depression 6 and 9 h after a single extradural dose of morphine.
17	75	L2–3	Morphine 2 mg 5 h after anaesthesia.	Small dose of opiate as premedication and 10 mg of morphine s.c. 3 h after extradural morphine.	Ventilatory depression 9 h after the extradural dose. Naloxone repeated twice within 4 h.	Ventilatory depression after concomitant use of extradural and parenteral morphine.
18	78	Th7–8	Morphine 5 mg 10 and 20 h after anaesthesia.	0.8 mg of leptanal during op. of aortic aneurysm.	Ventilatory depression requiring naloxone once 6 h after last dose of extradural morphine.	Ventilatory depression after two repeated injections of extradural morphine.
19	79	L3–4	3 mg 7 h after anaesthesia.	Small doses of opiates as premedication and 10.5 h after anaesthesia.	Ventilatory depression 7.7 h after extradural morphine. Naloxone given four times within 3 h.	Ventilatory depression induced by concomitant use of extradural and parenteral opiates in a septic patient.

TABLE III. *Patients with cancer or trauma experiencing ventilatory depression after extradural morphine* (n = 4)

Patient	Age (yr)	Level of catheter	Extradural morphine	Parenteral	Clinical course	Comment
20	55–60	Thoracic	Morphine 2 mg	24 h before extradural morphine, moderate doses of opiates in parenteral form because of rib fractures.	Within 30 min after extradural morphine, ventilatory depression. Naloxone given once.	Ventilatory depression after a small extradural dose of morphine in a patient given moderate systemic doses of opiates and with multiple rib fractures.
21	68	Thoracic	Morphine 2 mg	During 4 h before extradural morphine, high doses of parenteral opiates to treat pain caused by rib fractures.	Within 30 min after extradural morphine, ventilatory depression. Naloxone given once.	Ventilatory depression after a small extradural dose of morphine in a patient given repeated systemic doses of opiates and with multiple rib fractures.
22	72	Thoracic	Morphine 2 mg	Two high doses of parenteral opiates 1–2 h before extradural morphine.	Within 30 min after extradural morphine, ventilatory depression. Naloxone given once.	Ventilatory depression after a small extradural dose of morphine in a patient given repeated systemic doses of opiates and with multiple rib fractures.
23	75	Lumbar	Day 1: 2 mg × 2, sacral route. Days 2–3: 2 mg × 3, lumbar route. Days 4–11: 1 mg × 3.	Day 3: single doses of parenteral opiates. Days 8–11: methadone orally, doses not known.	Day 11 unconscious, ventilatory depression, one dose of naloxone. After cessation of extradural and oral doses of opiates, pain free for 1 week.	Ventilatory depression induced by accumulation of methadone in a patient concomitantly treated with extradural morphine.

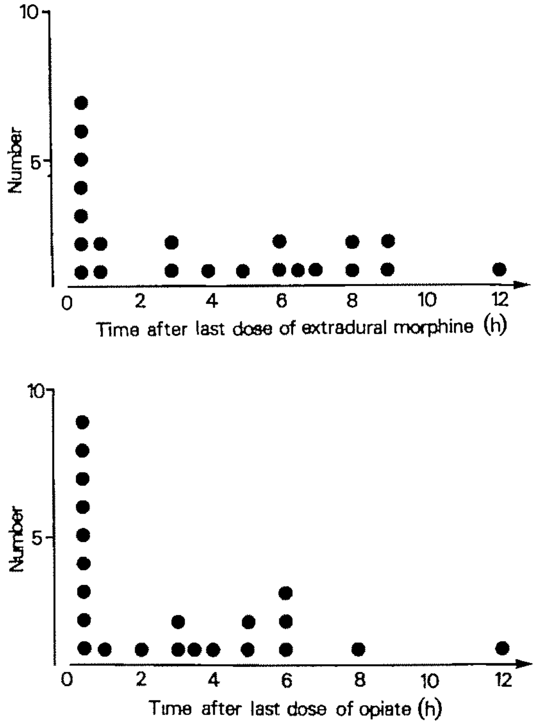

FIG. 2. Hours between the administration of the last dose of extradural morphine (upper legend) and the last dose of opiates (s.c., i.m., i.v. or extradural) (lower legend) and the occurrence of ventilatory depression requiring naloxone (22 patients).

Severe pruritus. Severe pruritus after extradural morphine was reported by 18 departments. Six reported a frequency less than 2%, two between 2 and 5% and six a frequency greater than 5%.

Urinary retention. The stated frequency of patients requiring bladder catheterization varied from 0.3 to 25% with a median value of 10%.

Other adverse effects. Neurological sequelae after administering morphine were not observed. Reports of single patients experiencing nausea or vomiting euphoria, anxiety or hallucinations were obtained from 11 departments.

One patient, 78 yr of age, underwent transurethal diathermy resection of the prostate under extradural anaesthesia with mepivacaine. Three hours after anaesthesia he was given a single dose of morphine 2 mg. Ten to 20 minutes after that injection the patient hallucinated, shivered and became unconscious. The respiratory rate, arterial pressure and heart rate, and the electrolyte concentrations in plasma were normal. The symptoms disappeared within 5–10 min without treatment.

Use of intrathecal opiates

Of the 10 departments in which intrathecal morphine was used only three were still using the method. Between 90 and 150 patients had been treated.

Six departments had observed adverse effects, the most frequent being ventilatory depression. After 0.8–2.0 mg of extradural morphine before cholecystectomy or total hip replacement, six of 32 patients developed $P\text{CO}_2$ greater than 7 kPa more than 8 h after anaesthesia. Five of these patients received naloxone. In 10 of the 12 that underwent cholecystectomy the lungs were artificially ventilated for at least 1.5 h after operation. (These 32 patients have been reported by Gjessing and Tomlin (1981).) One patient undergoing transvesical prostatectomy developed ventilatory depression 8 h after morphine 4 mg. He required repeated doses of naloxone for 8 h and thereafter artificial ventilation for another 12 h.

DISCUSSION

In 1976 a study on the effectiveness of intrathecal morphine for relief of experimental pain in rats was published (Yaksh and Rudy, 1976). This report initiated a series of trials in man in which long lasting pain relief (24–36 h) was observed after small doses of extradural or intrathecal morphine (Bahar et al., 1979; Wang, Nauss and Thomas, 1979). The use of these methods spread rapidly (Editorial, 1980) and became clinically accepted long before data from controlled studies were published.

Our survey further supports the impression of widespread use of these methods in clinical practice. Three years after publication of the original animal study (Yaksh and Rudy, 1976) a majority of the departments of anaesthesia in Sweden had used opiates extradurally.

The standard dose of morphine for extradural use was similar among different departments with a tendency to use smaller doses when the drug was given at the thoracic level. It is, however, not known if it is optimal to treat different postoperative pain conditions with the same standard dose. The infrequent use of morphine extradurally for obstetric pain may be attributed to the disappointing clinical results (Husemeyer, O'Connor and Davenport, 1980; Nybell-Lindahl et al., 1981). Our results underline the necessity to perform controlled clinical studies to define the dose and schedule of administration of morphine extradurally under different pain conditions.

Late ventilatory depression was reported in 4–7% of patients treated with intrathecal morphine. Higher figures have been reported in prospective studies (Davies, Tolhurst-Cleaver and James, 1980; Gjessing and Tomlin, 1981). Interestingly, in one recent study none of 440 patients developed ventilatory depression when 0.3 or 0.4 mg of morphine was administered intrathecally for postoperative pain relief (King et al., 1981). Thus, it may be possible to decrease the occurrence of ventilatory depression by administering smaller doses.

This is the largest survey so far reported on ventilatory depression after extradural morphine. This potentially life-threatening side-effect was reported in 0.25–0.40% of the patients in our sample. However, this figure is certainly an underestimate as the study was retrospective.

Nine of the 22 patients who developed ventilatory depression within 1 h after the last dose of extradural morphine received both extradural and systemic doses of opiates. Even if the concentration of morphine is reported to be small in plasma after extradural administration, it may induce ventilatory depression when a systemic dose of opiate is administered concomitantly (Weddel and Ritter, 1981).

Five of seven patients who developed ventilatory depression later than 6 h after the last dose of extradural morphine (patients Nos 11, 13, 15, 17, 19) received systemic doses of opiates also. Restricted use of systemic opiates when patients are treated with extradural morphine may reduce the risk of this dangerous late ventilatory depression (Boas, 1980; Reiz and Westberg, 1980; Gustafsson, Feychting and Klingstedt, 1981).

Other risk factors seemed to be an age of 70 yr or more, impaired respiratory function (patients Nos 3, 20–22) and thoracic administration. Only two of 22 patients developed depression later than 6 h after opiate administered by any route. In these cases (patients Nos 8, 17) high doses of morphine were given (tables I, II). This indicates that the extradural administration of morphine is reasonably safe if certain clinical factors are taken into consideration. More than 6 h after the last opiate administration (s.c., i.m., i.v. or extradural), the risk of ventilatory depression was greatly reduced. This does not mean that it is safe to give a further dose of opiate systemically more than 6 h after the last dose of extradural morphine. One patient developed respiratory depression when morphine was given systemically 8 h after the last extradural dose.

ACKNOWLEDGEMENTS

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EFFETS DELETERES DES OPIACES ADMINISTRES PAR VOIE SOUS- ET PERIDURALE: RESULTATS D'UNE ENQUETE NATIONALE EN SUEDE

RESUME

La Société Suédoise d'Anesthésiologie a mené une enquête nationale rétrospective sur l'expérience clinique de l'utilisation sous- et péridurale des opiacés. Une attention toute particulière s'est portée sur la fréquence et le type de la dépression respiratoire. Quatre-vingt-quatre-départements sur 93 ont répondu au questionnaire (90%). Jusqu'au mois de mai 1981, de la morphine a été administrée par voie péridurale à environ 6000–9150 patients, de la péthidine par voie péridurale à 220–450 patients et de la morphine intrathécale à 90–150 patients. Une dépression respiratoire nécessitant un traitement par la naloxone a été décrite chez 23 patients traités par la morphine pa voie péridurale (0,25–0,40%) et chez six patients traités par la morphine par voie intrathécale (4–7%). Chez 22 patients, l'administration de morphine par voie péridurale a été considérée comme un facteur principal ou aggravant de survenue d'une dépression respiratoire. Seuls deux patients parmi ces 22 ont objectivé cette dépression respiratoire plus de 6 h après la dernière dose d'opiacé (s.c., i.m., i.v. ou péridurale). Il semble y avoir eu une sur-représentation de patients de 70 ans et plus, de patients ayant subi une analgésie péridurale dorsale et de patients ayant une capacité respiratoire diminuée.

GEFÄHRLICHE NEBENWIRKUNGEN VON PERIDURALER UND INTRATHEKALER ANWENDUNG VON OPIATEN: BERICHT ÜBER EINE LANDESWEITE RETROSPEKTIVE UNTERSUCHUNG IN SCHWEDEN

ZUSAMMENFASSUNG

Die Schwedische Gesellschaft für Anästhesie führte eine landesweite retrospektive Untersuchung über die klinischen Erfahrungen mit der epiduralen und intrathekalen Verabreichung von Opiaten durch. Das besondere Interesse galt der Häufigkeit und der Art einer dabei auftretenden Atemdepression. Den Fragebogen beantworteten 84 von 93 Abteilungen (90%). Bis zum Mai 1981 hatten 6000 bis 9150 Patienten Morphium epidural, ca. 220 bis 450 Patienten epidural Pethidin und 90 bis 150 Patienten intrathekal Morphium erhalten. Über das Auftreten einer Atemdepression, die Behandlung mit Naloxon erforderlich machte, wurde bei 23 Patienten, denen epidural Morphium 0,25–0,40% und bei 6 Patienten, denen intrathekal Morphium 4–7% verabreicht worden war, berichtet. Bei 22 Patienten nahm man an, daß die Verabreichung von epiduralem Morphium den hauptsächlichen oder einen zusätzlichen Faktor für das Auftreten einer Atemdepression darstellte. Nur zwei von diesen 22 Patienten hatten später als 6 Stunden nach der letzten Opiatdosis (s.c., i.m., i.v. od epidural) eine Atemdepression. In der Gruppe mit Atemdepression befanden sich vermehrt Patienten, die 70 Jahre oder älter waren, oder bei denen eine Epiduralpunktion in der Thorakalregion durchgeführt worden war oder solche mit eingeschränkter Lungenfunktion.

EFECTOS ADVERSOS DE LOS OPIATOS EXTRADURALES E INTRATECALES: INFORME DE UN ESTUDIO EFECTUADO EN SUECIA A ESCALA NACIONAL

SUMARIO

La Sociedad Sueca de Anestésicos ha llevado a cabo un estudio restrospectivo a nivel nacional al respecto de las experiencias clínicas con los opiatos de administración extradural e intratecal. Se emplazó un interés especial sobre la frecuencia y el tipo de depresión respiratoria. El cuestionario lo contestaron 84 de los 93 departamentos contactados (90%). Hasta el mes de mayo de 1981 se había administrado morfina extradural a entre 6000 y 9150 pacientes, petidina extradural a entre 220 y 450 pacientes y morfina intratecal a entre 90 y 150 pacientes. Se informó el uso de naloxano como tratamiento de la depresión respiratoria en 23 pacientes tratados con morfina extradural (0,25–0,40%) y en seis a los que se les administró morfina intratecal (4–7%). En 22 de los pacientes la administración de morfina extadural se consideró como un factor principal o contribuyente a la aparición de depresión respiratoria. Tan sólo dos de los 22 pacientes experimentaron depresión respiratoria después 6 horas de haber administrado la última dosis de opiatos (subcutánea, intramuscular, intravenosa o extradural). Parece ser excesiva la representación de pacientes de edad igual o superior a los 70 años, la de aquellos que recibieron inyección toráctica extradural y la de aquellos con capacidad ventiladora reducida.

Br. J. Anaesth. (1982), 54, 487

MATERNAL AND FETAL CONCENTRATION OF MORPHINE AFTER INTRATHECAL ADMINISTRATION DURING LABOUR

J. P. BONNARDOT, M. MAILLET, J. C. COLAU, F. MILLOT AND P. DELIGNE

SUMMARY

Twenty-five healthy women in labour received morphine 1–1.75 mg in normal saline intrathecally. The residual pain was evaluated on a scale from 0 to 5 at 10 min (score 2.5) and at 25 min (score 1.5). After delivery the maternal and fetal plasma morphine concentrations were measured by radioimmunoassay in 14 parturients. Twenty-three women of 25 had vaginal deliveries, 20 of them without forceps. The maternal and fetal plasma concentrations of morphine were 6 ng ml^{-1} or less. The intrathecal (but not extradural) administration of morphine is effective and could provide an interesting alternative for pain relief in labour.

The recent use of intrathecal morphine in labour has been the subject of much debate. The failures observed seem to involve extradural (Husemeyer, O'Connor and Davenport, 1980; Nybell-Lindahl et al., 1981) and not intrathecal administration (Scott et al., 1980; Baraka, Noueihid and Hajj, 1981). The aim of this investigation was to verify by clinical observation and by measurement of maternal and fetal plasma concentrations that intrathecal morphine is safe and effective.

SUBJECTS AND METHODS

Twenty-five healthy young women in labour, the majority primiparous ($n = 14$) and at term (39 weeks 5 days ± 1 week 3 days) were given morphine after their informed consent had been obtained. In all cases the presentation was cephalic. Analgesia was provided when the cervix was 2–4 cm dilated depending on the indication—comfort ($n = 8$), induced labour ($n = 14$), cervical dystocia ($n = 8$).

Preservative-free morphine hydrochloride 1–1.75 ml in normal saline (1 mg ml^{-1}) was injected intrathecally at the third lumbar interspace using a strict aseptic technique. Since morphine acts by saturating the active spinal sites (Samii et al., 1979), a dose related to the height of the patient as for extradural block (table I) rather than on an mg kg^{-1} basis, was preferred (Bonnardot et al., 1981).

TABLE I. *Dosage of morphine related to the height of the parturient (0.8 mg m^{-1}, 0.02 mg kg^{-1})*

Height (cm)	Morphine (mg)
<150	1.00
150–160	1.25
160–170	1.50
>170	1.75

The patients were kept supine for 5 min and then positioned 30° head up at the beginning of labour, increasing to 60° at the end. The parturient estimated the degree of pain after injection using a score of 5 to 0 where 5 represented the most acute pain felt during the last uterine contractions.

Maternal and fetal blood samples were taken immediately after 14 deliveries (12 primiparous women, two multiparous) which occurred at times most suitable for handling the samples (that is, during the day). Plasma concentrations were measured by radioimmunoassay (Berkowitz, 1976) after separating the morphine base from its metabolites by liquid–solid chromatography (Sandouk, 1980).

RESULTS

All parturients had relief from pain until delivery and probably into the post-partum period; two multiparous women did not suffer the pain of their post-partum uterine contractions as they had done after their previous deliveries. These results were similar to those obtained using the same method for postoperative analgesia (18–22 h pain relief in our own experience in gynaecological surgery).

The score for remaining pain was 2.5 at 10 min and 1.5 at 25 min. A minimal degree of discomfort which was easily tolerated persisted until delivery.

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The cervix became soft when it had been thick and tense, rarely remaining constricted. Twenty-three women had vaginal deliveries, 20 of which were spontaneous. Two women required Caesarean section and this was not related to the method of analgesia. All the neonates, 15 males and 10 females, were alive at birth. Twenty-two Apgar scores were 9 or better. The three scores of 8, 7 and 5 were related to misplaced umbilical cords. Maternal side-effects included itching ($n = 18$), somnolence ($n = 15$), nausea and vomiting ($n = 8$), retention of urine ($n = 3$) and headache ($n = 4$). In three patients the headaches were similar to those observed after accidental dural puncture with the extradural technique. In the other patients a slight frontal headache, which lasted for 48 h, occurred. No haemodynamic changes and no respiratory depression, either immediate or delayed, could be observed in the mothers or children.

Irrespective of the time of feto–maternal blood sampling following the administration of morphine (from 85 to 305 min), the plasma concentrations were 6 ng ml^{-1} or less (fig. 1). The relationship between the maternal and fetal concentrations was reversed with time. The transfer of morphine from c.s.f. to maternal blood seemed rapid, a low plasma concentration decreasing quickly to zero. In the neonates plasma concentrations increased with time, but remained very small.

DISCUSSION

With maternal plasma concentrations of 6 ng ml^{-1} the direct spinal action of morphine is proved. Sedation as a result of vascular redistribution would be associated with plasma concentrations greater than 30 ng ml^{-1}. A favourable change in the perception of pain seems to result from the cephalad spread of a small quantity of morphine diffusing through the c.s.f. Pulmonary hypoventilation did not occur. More than 50 ng ml^{-1} of morphine in plasma would have been necessary for alveolar hypoventilation to be present. In the same way, no neonatal respiratory depression occurred as a result of these low plasma concentrations. This lack of toxicity cannot be guaranteed with the extradural administration of morphine because the proximity of the dilated extradural venous plexus results in the rapid reabsorption of morphine with a high placental transfer and puts the fetus at risk for a limited analgesic benefit similar to that observed after i.m. administration (Chauvin et al., 1981).

The main side-effect in this study was headache and occurred at the beginning of the study. The initial injections were made after several dural punctures and the c.s.f. leak (and headache) observed after one puncture with a 17-s.w.g. needle could be compared to three punctures with a 25-s.w.g. needle. The frequency of this side-effect appears to be reduced with improved technique in our later cases.

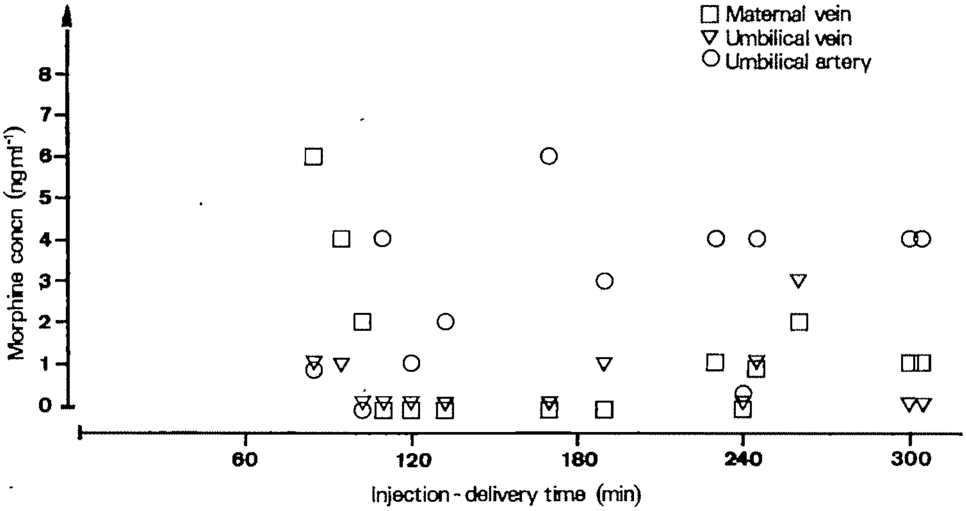

FIG. 1. Maternal and fetal concentrations (radioimmunoassy) ($n = 14 \times 3$; 40 samples, two unsuccessful attempts to take a sample of umbilical arterial blood) after intrathecal administration of morphine hydrochloride 0.8 mg ml^{-1}. The ratio of maternal : fetal plasmic concentrations of morphine were reversed with injection – delivery time; maximum rates being equal to or less than 6 ng ml^{-1}.

The mother's head was hyperextended during injection and maintained normally for the remainder of labour. This resulted in a caudad then cephalad movement of the meninges, helping to dissociate the holes through the fibres at the puncture site and thus restrict the leak of c.s.f.

The small feto–maternal plasma concentrations should encourage obstetric teams to use intrathecal morphine analgesia which could provide an interesting alternative when a conduction block is contraindicated during labour.

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CONCENTRATIONS MATERNELLE ET FOETALE DE MORPHINE APRES ADMINISTRATION INTRATHECALE AU COURS DU TRAVAIL

RESUME

Vingt-cinq femmes en bonne santé ont reçu, pendant leur travail, 1–1,75 mg de morphine diluée dans du sérum physiologique, par voie sous-durale. La douleur résiduelle a été évaluée selon une échelle allant de 0 à 5 après 10 min (résultat 2,5) et aprés 25 min (résultat 1,5). Après l'extraction, les concentrations plasmatiques de morphine maternelle et foetale ont été mesurées par une technique radio-immunologique. Vingt-trois femmes sur 25 ont accouché par voie basse, et 20 d'entre elles sans forceps. Les concentrations plasmatiques maternelles et foetales étaient de 6 ng ml^{-1} ou moins. L'administration intrathécale (mais pas péridurale) de morphine est efficace et pourrait offrir une alternative intéressante pour l'analgésie au cours du travail.

MÜTTERLICHE UND FÖTALE PLASMAKONZENTRATIONEN VON MORPHIUM NACH INTRATHEKALER ANWENDUNG UNTER DER GEBURT

ZUSAMMENFASSUNG

25 gesunde Frauen erhielten bei der Geburt 1–1,75 mg Morphium in physiologischer NaCl.-Lösung. Anhand einer Skala, die von 0 bis 5 reichte; wurden nach 10 (score 2,5) und nach 25 min (score 1,5) die Schmerzempfindungen gemessen. Nach der Ent bindung bestimmten wir die Plasmamorphiumkonzentration mit der Radioimmunassay-Methode im Blut von Mutter und Kind. 23 von 25 Frauen entbanden vaginal, davon 20 ohne Zangen. Die Plasmakonzentrationen im mütterlichem und kinlichem Plasma waren 6 ng ml^{-1} oder weniger. Die intrathekale (aber nicht Peridurale) Anwendung von Morphium ist wirksam und könnte eine interessante Alternative für die Schmerzbekämpfung bei der Geburt darstellen.

CONCENTRACION DE MORFINA EN LA MADRE Y EN EL FETO DESPUES DE LA ADMINISTRACION INTRATECAL DURANTE EL PARTE

SUMARIO

Veinticinco pacientes sanas recibieron, durante el parto, 1–1,75 mg de morfina en disolución salina normal, intratecalmente. El dolor remanente se evaluó en una escala graduada de 0 a 5 a los 10 min (puntuación 2,5) y a los 25 min (puntuación 1,5). Las concentraciones de morfina en el plasma de la madre y del feto se midieron, después del parto, mediante evaluaciones radioinmunológicas. Veintitres de las veinticinco mujeres tuvieron parto vaginal, no necesitando forceps 20 de ellas. Las concentraciones en el plasma del feto y de la madre fueron iguales o inferiores a los 6 ng ml^{-1}. La administración intratecal (pero no extradural) de morfina es efectiva y podría proveer una alternativa interesante para aliviar el dolor durante el parto.

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BLOOD LOSS IN TOTAL HIP REPLACEMENT: EXTRADURAL *v.* PHENOPERIDINE ANALGESIA

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SUMMARY

The effects of phenoperidine and extradural analgesia on blood loss during and after total hip replacement were compared in 41 patients randomly divided into two statistically comparable groups. Mean blood loss in patients who received phenoperidine was 1065 ± 316 ml and in patients who received extradural analgesia with 0.5% bupivacaine with adrenaline 1:200 000 it was 650 ± 277 ml ($P < 0.001$). There was no significant difference in postoperative blood loss between the two groups. The reduction in blood loss resulting from the extradural block may prove beneficial in decreasing the hazard and cost of blood transfusions and in facilitating autologous transfusion.

Total hip replacement (Charnley, 1979) is considered the procedure of choice for radical treatment of osteoarthritis and rheumatoid arthritis of the hip. There are two major complications of this procedure: haemorrhage and thromboembolism. The operation has a mortality rate of 1–2% and most deaths are secondary to postoperative pulmonary thromboembolism.

Previous studies of elective surgical procedures have confirmed the advantage of extradural anaesthesia over other techniques. It reduces operative blood loss (Keith, 1977), endocrine metabolic response to surgical stress (Kehlet, 1978; Harari et al., 1980) and the risk of thromboembolism (Modig et al., 1979). Extradural anaesthesia also improves postoperative Pa_{O_2}, the physical and mental state of the patient (Hole, Teajesen and Beeivik, 1980), and nitrogen balance (Brandt et al., 1978).

However, concern has been expressed about the adequacy of surgical muscle relaxation following extradural anaesthesia, and the patient's discomfort after more than 1 h of lateral decubitus position. (Those operated on under extradural anaesthesia complain of pain in the dependant shoulder and at sites of i.v. infusions.)

To reassess extradural anaesthesia and study its effect on operative blood loss in patients undergoing total hip replacement, we performed a prospective, randomized study, comparing operative blood loss in two groups of patients operated on under light general anaesthesia supplemented with either an extradural block or phenoperidine analgesia.

METHODS

We studied 41 patients, ASA class I and II (23 females and 18 males; age 45–86 yr) with advanced osteoarthritis of the hip who were to undergo total hip replacement. (One patient had both hips replaced over a 1-month interval.) Patients with rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and with previous hip operations were excluded from the study. Almost 60% of patients in both groups were receiving indomethacin, sulindac or diclofenac before operation.

Laboratory investigations before operation included full blood count and coagulation screen, plasma electrolyte concentration, chest x-ray, and e.c.g. Laboratory data for all patients were normal with no evidence of recent disease.

Patients were allocated randomly to two groups of 20. The patient with bilateral hip replacement was operated on once with extradural anaesthesia and once with phenoperidine.

All surgical procedures were performed by the same orthopaedic surgeon who was not informed of the anaesthetic technique. Surgery was performed in the lateral position using a posterolateral approach. A ceramic-type prosthesis was used and both the acetabular and the femoral prostheses were fixed with acrylic cement.

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Anaesthesia technique

Premedication consisted of atropine 0.5 mg, trimeprazine 0.25 mg kg^{-1} and meperidine 1 mg kg^{-1} given i.m. 1 h before induction of anaesthesia.

In group I patients, anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. Suxamethonium 1 mg kg^{-1} was given i.v. to facilitate tracheal intubation. The lungs were ventilated mechanically using a Manley ventilator and a gas mixture of nitrous oxide 4 litre min^{-1} and oxygen 3 litre min^{-1}. Subsequent analgesia and muscle relaxation were achieved with phenoperidine and pancuronium given i.v. as required. The last doses of phenoperidine and pancuronium were administered approximately 45–60 min before the end of surgery. Residual muscle paralysis was antagonized with atropine and neostigmine.

In group II patients, anaesthesia was also induced with thiopentone 4–5 mg kg^{-1} i.v. Suxamethionium 1 mg kg^{-1} was also administered i.v. to facilitate tracheal intubation and the lungs were mechanically ventilated using a Manley ventilator and a gas mixture of nitrous oxide 4 litre min^{-1} and oxygen 3 litre min^{-1}. Pancuronium was given to facilitate mechanical ventilation. Patients were then placed in a flexed lateral position with the side to be operated on lowermost. Extradural anaesthesia was administered through a 17-gauge Tuohy needle at L3–4 interspace; one dose of 0.5% bupivacaine with adrenaline 1 : 200 000 was injected, the dose having been calculated in relation to age and size of patients 64.5 ± 5.5 mg). Fifteen minutes later, patients were placed in position for surgery. An infusion of Ringer's lactate was used to supplement maintenance fluid intake; blood loss greater than 10% of calculated blood volume was replaced with packed red blood cells. Heparin 1250 u. every 3 h was given starting immediately after surgery for a period of up to 10–15 days on average.

Operative blood loss was estimated from the increase in weight of swabs and towels and the contents of suction bottles. For 36 h after operation, blood draining from the wound was collected in closed vacuum bottles. Haemoglobin concentrations and haematocrits were estimated on the 1st and 6th days after operation. The results for each group were compared using Mann–Whitney tests.

Platelet count and partial thromboplastin time were also estimated on the 1st and 6th days after operation.

RESULTS

Both groups were statistically comparable with regard to age, sex and physical status before operation (table I), but height and weight of patients were statistically greater in group II (extradural) patients. The average duration of surgery was not statistically different between the two groups; 102 ± 11 in group I and 101 ± 14 in group II (min). There was no significant difference in sizes of prostheses between the two groups.

Blood loss during and after operation in the two groups are shown in table II and figure 1. The mean blood loss during operation in group I patients (phenoperidine) was 1065 ± 316 ml. Mean blood loss during operation in group II patients (extradural) was 650 ± 277 ml ($P < 0.001$). During the period after operation, there were no differences in blood loss between both groups (table II). Haemoglobin and haematocrit values taken on the 1st and 6th days after operation did not show any difference between the two groups (table III). Mean changes in arterial pressure were the same in both groups, decreasing 20–30% below values before operation. Coagulation screen was normal in all patients.

DISCUSSION

Both groups of patients were statistically comparable although weight and height were

TABLE I. *Details of patients before operation*

	No. of patients	Sex M	Sex F	Mean wt. (kg)	Mean ht. (cm)
Group I (phenoperidine)	21	9	12	59.2 ±6.3	160.1 ±7.8
Group II (extradural)	21	10	11	66.3 ±9.8	164.9 ±3.8

TABLE II. *Mean blood loss*

	During operation	First 24 h after operation	24–36th h after operation
Group I (phenoperidine)	1065±316	509±270	27±50
Group II (extradural)	650±277 ($P<0.001$)	545±122 (n.s.)	4.6±15 (n.s.)

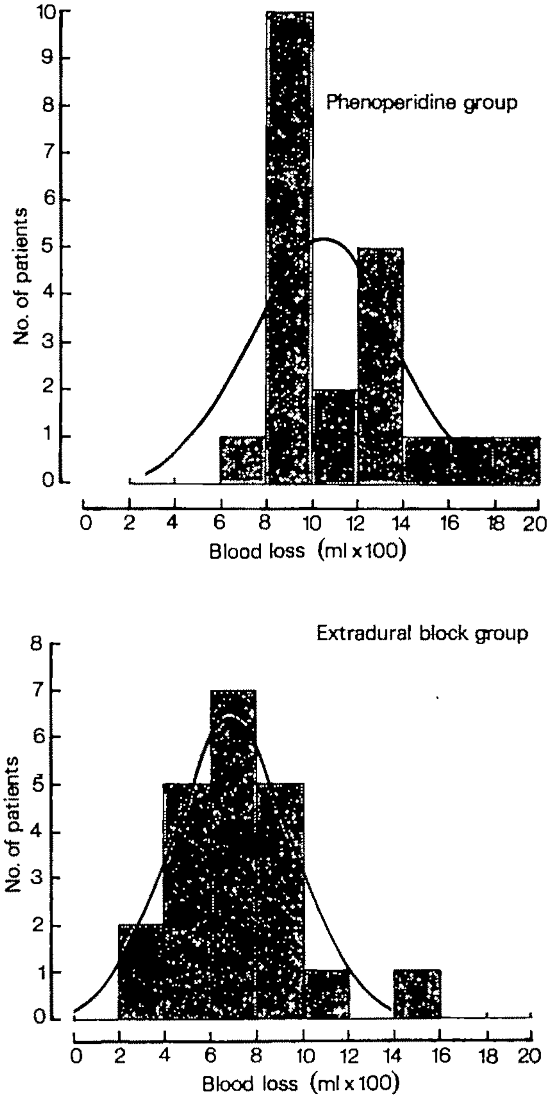

FIG. 1. Distribution of blood loss in the two groups of patients.

greater in the extradural group. Large variations in operative blood loss can occur even among patients of the same study group. These variations are mainly secondary to the patients' anatomico-physiological states and chronobiological changes (Radzialowski and Bousquet, 1968; Scheving, von Mayersbach and Pauly, 1974), or can be a result of different operative techniques if more than one surgeon is involved (Hole, Teajesen and Beeivik, 1980). Large variations in operative blood loss have also been reported when the same surgeon has performed identical procedures (Hercus et al., 1961). In our series, operative blood loss varied from 800 to 1900 ml in the phenoperidine group and from 300 to 1400 ml in the extradural group. One surgeon performed the same surgical procedure in both groups.

Gravimetric methods for determination of operative blood loss are simple, reliable and used commonly (Gouin, Dessemond and Benoit, 1978). Their reliability, however, compared with colorimetric techniques, electronic conductivity techniques and blood volume measurements, remains to be determined. Arterial pressure decreased by 20–30% from values before operation in both groups. The mechanisms involved in the smaller operative blood losses in the extradural group are not completely understood. These may include:

Redistribution of circulating blood volume secondary to reduction in hydrostatic pressure;

vasodilatation of arteries, arterioles and veins in the area affected by the extradural block with gravitational emptying of the blood vessels in the lateral position from the uppermost operative site;

shunting of blood away from muscles and bones to subcutaneous tissue and skin (Cousin and Wright, 1971);

compensatory vasoconstriction of the operative site (Bond, 1969). A combination of these effects may occur.

Controlled ventilation during general anaesthesia may cause an increase in intrathoracic pressure (Moir, 1968). This leads to diminished venous return from the periphery and an increase of venous pressure which may cause increased bleeding during hip replacement. In our study, we combined controlled ventilation with extradural anaesthesia. This resulted in a significant reduction in operative blood loss ($P<0.001$) compared with the other group of patients whose controlled ventilation was supplemented with i.v. injections of phenoperidine.

TABLE III. *Postoperative haematocrit and haemoglobin*

	1st day after operation		6th day after operation	
	Haematocrit	Haemoglobin	Haematocrit	Haemoglobin
Group I (phenoperidine)	38±2.9	13.51±1.05	37.5±2.6	13.27±1.18
Group II (extradural)	39±3.9	13.70±1.25	38.8±3.3	13.28±9.70

Extradural anaesthesia probably offset the effect of controlled ventilation on the peripheral venous pressure by causing peripheral vasodilatation. Also, light general anaesthesia induced before performing the extradural block allows smooth and painless positioning of the patient.

We believe that significant reduction in operative blood loss can be achieved through appropriate selection of extradural anaesthesia for patients undergoing hip replacement. The reduced need for blood transfusion can be successfully met by autotransfusion techniques in which 900–1200 ml of blood can be stocked by the Piggback autologue transfusion technique (Ellison and Wurzel, 1975) hence reducing the risks and cost of large blood transfusion.

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EFFETS COMPARES DE L'ANALGESIE PAR VOIE PERIDURALE ET DE L'ANALGESIE A LA PHENOPERIDINE SUR LES PERTES SANGUINES DANS LES PROTHESES TOTALES DE HANCHE

RESUME

Nous avons comparé les effets de la phénopéridine et de l'analgésie péridurale sur les pertes sanguines pendant et après prothèse totale de hanche chez 41 patients répartis au hasard en deux groupes statistiquement comparables. La perte sanguine moyenne s'est élevée à 1065±316 ml chez les patients qui recevaient de la phénopéridine et à 650±277 ml chez ceux qui recevaient une analgésie péridurale avec de la bupivacaïne à 0,5% adrénalinée au 1/200 000 ème ($P<0{,}001$). Il n'y a pas eu de différence significative entre les deux groupes pour ce qui est de la perte sanguine post-opératoire. La réduction du saignement obtenue par le bloc péridural peut être un avantage car elle diminue les risques et le coût de la transfusion, et facilite les transfusions autologues.

BLUTVERLUST BEI HÜFTGELENKSTOTALENDOPROTHESEN: VERGLEICH DER ANALGETISCHEN WIRKUNG VON PERIDURALANÄTHESIE UND PHENOPERIDIN

ZUSAMMENFASSUNG

Die Wirkung von Phenoperidin und Periduralanästhesie auf den Blutverlust während und nach Hüftgelenkstotalendoprothese wurde bei 41 Patienten verglichen, die wir nach Randomisierung in zwei statistisch vergleichbare Gruppen aufgeteilt haben. Der mittlere Blutverlust bei den Patienten mit Phenoperidin betrug 1065 ± 316 ml, während die Patienten mit Periduralanästhesie (0,5% Bupivacain mit Adrenalin 1:200 000) 650 ± 277 ($P<0.001$) ml Blut verloren. Es gab keinen signifikanten Unterschied im postoperativen Blutverlust zwischen den beiden Gruppen. Die Reduzierung des Blutverlusts, die sich aus der Periduralanästhesie ergibt, kann sich als günstig für die Senkung des Risikos und der Kosten von Bluttransfusionen, als auch für die Erleichterung der autologen Transfusion erweisen.

PERDIDA DE SANGRE EN LA SUSTITUCION TOTAL DE LA CADERA: USO FENOPERIDINA EN COMPARACION CON LA ANESTESIA EXTRADURAL

SUMARIO

Se compararon los efectos de la anestesia con fenoperidina en comparación con la anestesia extradural, en lo tocante a la pérdida de sangre durante la intervención quirúrjica tendente a la sustitución total de la cadera y después de dicha intervención, en 41 pacientes divididos de forma aleatoria en dos grupos estadísticamente comparativos. La pérdida media de sangre en los pacientes que recibieron fenoperidina fue de 1,065 ± 316 ml y para los pacientes que recibieron analgesia extradural con bupivacaína al 95% y con adrenalina en una proporción de 1:200,000 dicha pérdida fue de 650 ± 277 ml ($P<0,001$). No hubo diferencia estadísticamente significativa en la pérdida de sangre después de la operación entre los dos grupos. La reducción de la pérdida de sangre como resultado del bloqueo extradural puede que llegue a ser beneficiosa en lo relativo a la disminución del peligro potencial y del coste de las transfusiones sanguíneas y para facilitar las transfusiones autólpgas.

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EFFECT OF THE TRENDELENBERG POSITION ON SPINAL ANAESTHESIA WITH HYPERBARIC BUPIVACAINE

C. J. SINCLAIR, D. B. SCOTT AND H. H. EDSTRÖM

SUMMARY

In a double-blind study, the effect of the Trendelenberg position was compared with the supine, in 20 patients following intrathecal injection of 3 ml of 0.5% bupivacaine in 8% glucose. All patients had blocks suitable for abdominal surgery. Although the mean spread was greater in those patients tilted head-down, this was not statistically significant. The variation of the spread around the mean was greater in the head-down group, and blocks extended into the cervical region in two patients. There were no differences in motor block, duration or cardiovascular changes between the groups. It is concluded that the Trendelenberg position is not necessary to ensure spread of local anaesthetic solution into the mid-thoracic region for abdominal surgery.

Local anaesthetics for spinal anaesthesia are usually administered as hyperbaric solutions. One of the benefits claimed for hyperbaric solutions is that their spread can be controlled by posture. Standard texts (Moore, 1965; Lee and Atkinson, 1978) advocate the use of the Trendelenberg position to ensure spread of the hyperbaric local anaesthetic solution into the mid-thoracic region for abdominal surgery. This was thought necessary to ensure flow of the local anaesthetic solution down the lumbar curve into the thoracic concavity. The origin of this manoeuvre stems from work by Barker (1907), who studied the behaviour of hyperbaric solutions in a glass tube curved to reproduce the shape of the vertebral canal.

Recent work (Wildsmith et al., 1981), investigating the sitting and lateral positions, has suggested that posture is not as effective as was once thought. For example, sitting the patient upright during and for 2 min after the spinal injection resulted in a block only three to four segments lower than was achieved in the horizontal position. A lateral position maintained for 5 min resulted in a unilateral block, but this had become bilateral within 15 min of turning supine.

The present study was undertaken to determine the effect of a steep Trendelenberg position on the spread of blockade during spinal anaesthesia with 0.5% bupivacaine in 8% dextrose.

METHODS

Twenty female patients aged 30–69 yr, undergoing major gynaecological surgery for which spinal anaesthesia was thought appropriate, took part in this study. The nature of the study, which had approval from the local ethics committee, was explained and the patient's consent obtained. The 20 patients were allocated randomly to two groups of 10, one group to be tilted 15° head-down for 10 min immediately following injection of the local anaesthetic, the other to remain horizontal.

One hour before operation patients of less than 65 yr were given diamorphine 5 mg and atropine 0.6 mg and those older than 65 yr received diamorphine 2.5 mg and atropine 0.6 mg by i.m. injection. A standard mid-line lumbar puncture was performed using a 25-gauge needle in the L3–4 interspace. All lumbar punctures were performed with the patient in the right lateral position on a horizontal table. Three millilitre of 0.5% bupivacaine in 8% dextrose (sp. gr. 1.026 at 20 °C) was injected, without barbotage, over a period of approximately 15 s. This dose was chosen after considerable experience with hyperbaric bupivacaine in lower abdominal surgery. The needle was withdrawn, the patient immediately turned supine and the table adjusted to a 15° head-down tilt or left in the horizontal according to the randomized list. Ten minutes later all patients were positioned supine and horizontal.

The cephalad spread of analgesia (loss of appreciation of pin-prick) and anaesthesia (inability to appreciate touch), and motor block in the legs were assessed at 12, 15, 20, 25 and 30 min by an investigator who had no knowledge of the position of the patients in the first 10 min following spinal injec-

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tion. Motor block in the legs was graded on a 0–3 scale, 0 being no block, 1 = inability to raise the extended leg, 2 = inability to flex the knee and 3 = inability to flex the ankle. Arterial pressure and heart rate were measured every 2 min with a Dinamap 845 monitor (Applied Medical Research).

Thirty minutes after the spinal injection, seven patients undergoing lower abdominal surgery were anaesthetized with thiopentone followed by nitrous oxide in oxygen and 0.5% halothane, and the remaining 13 patients for vaginal surgery were deeply sedated with 0.8% chlormethiazole by continuous i.v. infusion. During surgery, any requirement for further analgesia or muscle relaxation was provided by increasing the concentration of halothane or the use of gallamine 40 mg and their use was noted.

Following recovery of consciousness, analgesia, anaesthesia and motor block were assessed every 15 min until regression of analgesia to L5, or full restoration of motor power. Duration of sensory block was assessed as the last time analgesia could be detected at the T12 and L5 dermatomes. It was possible to assess 16 patients (eight in each group) before the block had regressed to T12, and 18 patients (nine in each group) before regression to L5. In the two remaining patients operating time was greater than 4 h and there was no sensory deficit on recovery of consciousness. Similarly, recovery from motor block could only be assessed in 18 patients.

The results were analysed using Student's t test, $P<0.05$ being taken to indicate a significant difference.

RESULTS

There were no statistical differences in mean age, weight and height between the two groups (table I). In the head-down group, six patients underwent vaginal surgery and four had lower abdominal operations, compared with seven and three respectively in the horizontal group.

Sensory spread (figs 1 and 2). The mean spread of analgesia was greater in the head-down group although this difference was not statistically significant. There was a wider range in the head-down group (C4–T4) compared with the horizontal group (T2–T6), and two patients in the head-down group

TABLE I. *Mean (±SEM) age, weight and height in the two groups*

	Horizontal	Head-down
Age (yr)	50.6±3.7	44.5±3.9
Weight (kg)	63.8±2.4	66.6±3.1
Height (cm)	160.5±1.9	158.3±1.7

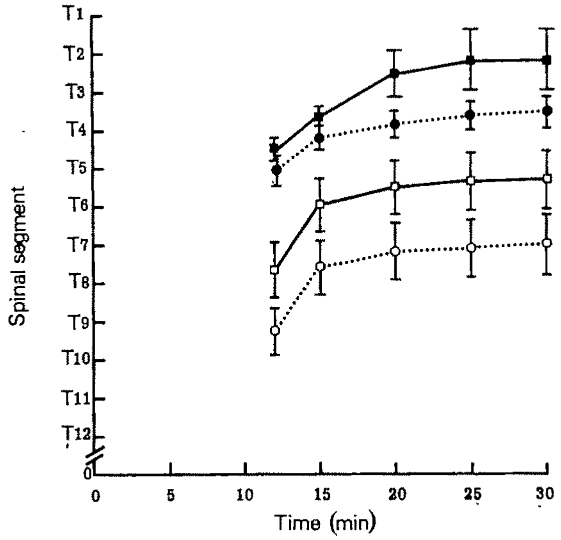

FIG. 1. Mean levels (± SEM) of anaesthesia and analgesia following subarachnoid injection in the two groups: ■——■ = analgesia and □——□ = anaesthesia in the head-down group; ●...● = analgesia and ○...○ = anaesthesia in the horizontal group.

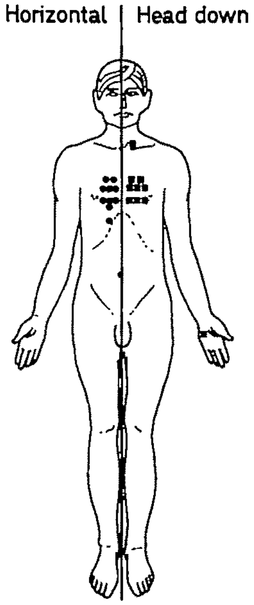

FIG. 2. Cephalad spread of analgesia, 30 min after subarachnoid injection, in the 10 patients in each group.

had spread into the cervical segments (C4 and C8).

Anaesthesia was also higher in the head-down group, although again this difference was not statistically significant. Analgesia to pin-prick was generally three to four spinal segments higher than anaesthesia.

Motor block. This was complete (grade 3) in eight patients in the horizontal group and nine in the head-down group. There was no difference in speed of onset.

Cardiovascular changes (table II). Arterial systolic pressure decreased by a mean of approximately 30 mm Hg in both groups over the first 30 min following spinal injection. There was no significant difference between the groups. The lowest systolic pressure recorded was 77 mm Hg. There was no correlation between spread of the block and decrease in arterial pressure.

TABLE II. *Cardiovascular changes. Mean (± SEM) arterial systolic and diastolic pressures before and after (mean lowest values) spinal block in the two groups. Mean (± SEM) heart rates before and after (mean most different from before block values) spinal block in the two groups*

	Horizontal	Head-down
Systolic pressure (mm Hg)		
Before block	132.4 ± 2.8	131.1 ± 5.2
Lowest value	98.8 ± 4.3	101.7 ± 3.4
Diastolic pressure (mm Hg)		
Before block	74.7 ± 3.8	79.4 ± 3.8
Lowest value	53.9 ± 3.4	56.4 ± 3.1
Heart rate (beat min^{-1})		
Before block	92.3 ± 3.3	87.2 ± 5.7
After block	81.7 ± 6.4	78.5 ± 6.1

Mean heart rates decreased by approximately 10 beat min^{-1}, but individual percentage changes ranged from −45% to +45%. The slowest recorded heart rate during the first 30 min following spinal injection was 59 beat min^{-1}.

Supplementary anaesthesia. Six of the seven patients undergoing abdominal surgery required, approximately 1.5–2 h after spinal injection, an increase of halothane to 1% and a small dose of gallamine to ensure satisfactory operating conditions.

Duration (table III). There were no significant differences between the groups. Duration of analgesia in the T12 dermatome was approximately 2.5 h, and in the L5 dermatome approximately 3–3.5 h. Motor power in the legs returned to normal after approximately 2.5–3 h. There was no prolongation of motor block after return of normal sensation in any patient.

TABLE III. *Mean (± SEM) duration of analgesia at the T12 and L5 dermatomes in the two groups*

	Horizontal	Head-down
Duration (min) at T12	145.3 ± 7.2	152.8 ± 7.2
Duration (min) at L5	193.3 ± 10.4	201.7 ± 11.5

Complications. Three patients in the head-down group complained of nausea during the first 30 min after spinal injection which responded to i.v. fluids. The patient with spread of analgesia to C4 was given ephedrine prophylactically. Before induction of general anaesthesia, she had no trouble maintaining spontaneous breathing, but ventilation was assisted for approximately 10 min following an i.v. induction dose of thiopentone. No patient experienced post-spinal headache.

DISCUSSION

Although the use of the Trendelenberg position increased the mean spread of analgesia, this was only of the order of one to two spinal segments, and was attributable to the fact that two patients had blocks extending into the cervical region. The other eight patients who were tilted had blocks comparable in height to the 10 who remained horizontal. We feel, therefore, that the use of the Trendelenberg position does not guarantee a higher spread of anaesthesia in an individual patient, but can occasionally cause unduly high spread.

A 15° head-down tilt does not sound excessive, but was in fact the maximum that our tilting trolley would allow. Any further degree of Trendelenberg would undoubtedly have been most uncomfortable for the conscious patient. In a previous study (Wildsmith et al., 1981) it was seen that the sitting position (90° head-up) only reduced the height of block by three to four spinal segments and the results of the present study are therefore not unexpected.

Bupivacaine 0.5% in 8% glucose was chosen for this study as we were interested in its potential as a new agent for spinal anaesthesia. We were able to confirm that this hyperbaric solution produces a satisfactory block for abdominal surgery, which is not always the case with the isobaric solution (Chambers, Edström and Scott, 1981). Although six of the seven patients undergoing abdominal operations required supplementary anaesthesia before the end of surgery, it must be remembered that we were allowing 30 min to assess the spinal block before surgery, which could have started much earlier in these patients. Hyperbaric bupivacaine, although achieving a high level of spread, is inclined to wear off quite rapidly compared with the isobaric solutions. A shorter duration is only to be expected with a wide spread, as less anaesthetic will be available for each nerve blocked. The average duration of the block before regression to T10 was 133 ± 5.9 min in those patients in whom it could be measured. This fits with the clinical observation that supplementation was required 90–120 min after the spinal injection.

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EFFET DE LA POSITION DE TRENDELENBERG SUR LA RACHIANESTHESIE A LA BUPIVACAINE HYPERBARE

RESUME

Nous avons étudié, dans un essai en double aveugle, l'effet de la position de Trendelenberg chez 20 patients, après l'injection intrathécale de 3 ml de bupivacaïne à 0,5% dans du glucose à 8%. Tous les patients avaient des blocs compatibles avec la chirurgie abdominale. Bien que l'extension moyenne soit plus grande chez les patients basculés tête en bas, ceci n'était pas statistiquement significatif. Les écarts par rapport à la valeur moyenne de l'extension étaient plus grands dans le groupe des patients basculés, et les blocs remontaient dans la région cervicale chez deux patients. Il n'y avait pas de différences de bloc moteur, de durée d'anesthésie ou de modifications hémodynamiques entre les deux groupes. Nous en concluons que la position de Trendelenberg n'est pas nécessaire pour assurer la diffusion de la solution anesthésque locale jusqu'à la région thoracique moyenne en chirurgie abdominale.

DIE WIRKUNG DER TRENDELENBERG-LAGERUNG AUF DIE SPINALANÄSTHESIE MIT HYPERBAREM BUPIVACAIN

ZUSAMMENFASSUNG

In einer Doppelblindstudie untersuchten wir bei 20 Patienten die Wirkung der Trendelenberg-Lagerung auf die intrathekale Injektion von 3 ml 0,5% Bupivacain in 5% Glucose. Alle Patienten hatten eine Blockade, die für die Bauchchirurgie ausreichte. Die mittlere Blockade-ausbreitung war bei den Patienten mit Kopftieflage gering, aber nicht signifikant höher. Die Abweichung von der mittleren Blockadeausbreitung war in der Gruppe mit Kopftieflage größer und bei zwei Patienten erreichte das Anästhesieniveau die Zervikalregion. Keinen Unterschied gab es bei der Blockade der Motorik, der Analgesiezeit und der Kreislaufwirkung zwischen den beiden Gruppen. Wir schließen daraus, daß die Trendelenberg-Lagerung nicht notwendig ist um die Ausbreitung des Lokalanästhetikums in die mittlere Thorakalregion, wie sie für die Bauchregion notwendig ist, zu gewährleisten.

EFECTO DE LA POSICION DE TRENDELENBERG EN LA ANESTESIA DE LA COLUMNA VERTEBRAL MEDIANTE BUPIVACAINA HIPERBARICA

SUMARIO

Se estudió en veinte paciente, en un estudio de doble anonimato, el efecto de la posición de Trendelenberg, a raíz de una inyección intratecal de 3 ml de 0,5% de bupivacaína en glucosa al 8%. Todos los pacientes sufrieron bloqueos adecuados para la intervencial abdominal. Aunque la dispersión media fue superior en aquellos pacientes inclinados con la cabeza hacia abajo, esto no fue estadísticamente significativo. La variación de la dispersión alrededor de la media fue superior en el grupo de cabeza a bajo, extendiéndose bloqueos en la región cervical de dos de los pacientes. No hubo diferencias en el bloqueo motriz ni en la duración, ni tampoco cambio cardiovasculares entre los diversos grupos. Se concluye que la posición de Trendelenberg no es necesaria para asegurar la dispersión de la solución anestésica local en la regíon toráctica media para fines de intervención quirúrjica abdominal.

Br. J. Anaesth. (1982), 54, 501

ANALGESIC RESPONSES TO I.V. LIGNOCAINE

R. A. BOAS, B. G. COVINO AND A. SHAHNARIAN

SUMMARY

The analgesic effect of i.v. lignocaine was evaluated in five patients with clinical neuralgic pain of varying aetiology. The response was compared with that on concurrently-induced ischaemic pain, initially of the same intensity. Following a high dose infusion of 3 mg kg^{-1} (lignocaine concentrations greater than 3 $\mu g\ ml^{-1}$) both pains were decreased, clinical pain to a significantly greater extent. Thereafter, at lower doses and blood concentrations, lignocaine was without effect on ischaemic pain, but almost totally suppressed the same patient's clinical pain. The results suggest a divergence in the specificity of the analgesic action of lignocaine i.v. according to the nature of the pain-inducing process. Disorders manifesting as deafferentation or central neuralgias appear to be affected favourably by lignocaine i.v., whereas pain of peripheral origin is unaffected by lignocaine, except at blood concentrations which approach toxic values.

The ability of lignocaine to suppress irritable foci in the heart and brain (Covino and Vassallo, 1976), has proved to be of value in the treatment of ventricular arrhythmias and epileptic seizures. Pain associated with neurological deafferentation may have spinal electrogram patterns characterized by high-frequency burst discharge activity in neurons of the central nervous system (Loeser, Ward and White, 1968; Anderson et al., 1971). Since this discharge activity may be similar in nature to ectopic activity in the heart or epileptic activity in the cerebral cortex it seemed worthwhile considering the use of lignocaine i.v. as an analgesic agent in patients presenting with appropriate features of neurological deafferentation disorders. Some support for this concept could be derived from earlier clinical experience in the treatment of pain of postherpetic neuralgia (Hatangdi, Boas and Richards, 1976).

PATIENTS AND METHODS

Five patients who had given written consent were chosen to participate in this initial investigation. All were from the Pain Clinic at the University of Massachusetts Medical Center. Each patient had severe pain for a minimum of 6 months before the study and was considered to have a disorder of a dominant neuralgic pattern with elements of central or spinal pain as judged by the known pathology and symptomatic features. The clinical disorders demonstrated by the five patients are shown in table I together with the ages and weights of the patients.

Catheters were placed in the antecubital vein and radial artery in one arm and a pneumatic tourniquet applied above the elbow on the opposite arm. The patients were trained to use a 10-cm linear analogue scale for depicting pain intensity. At the start of the study, each patient was asked to score the intensity of their clinical pain. Ischaemic pain was then induced by inflating the tourniquet to a pressure in excess of systolic arterial pressure and asking the patient to exercise the occluded arm until the ischaemic-induced pain was of equal intensity to their clinical pain. At that point lignocaine 3 mg kg^{-1} was administered i.v. over a 3-min period by means of a Harvard pump, followed by an infusion of lignocaine 4 mg min^{-1} for a period of 1 h. Arterial blood samples were taken before and immediately following the administration of the 3-mg kg^{-1} injection of lignocaine and at 1, 2, 3, 5, 10, 15, 30, 45 and 60 min during the infusion of lignocaine i.v. The scoring of the pain intensity for both clinical and ischaemic pains was undertaken simultaneously with the drawing of each blood sample. The concentration of lignocaine in whole blood was determined subsequently using a gas chromatographic technique as described by Kennaghan (1968).

Two modifications to the plan were required during the course of the study. In two instances the lignocaine infusion was curtailed before the last sampling time when signs of mild toxicity de-

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TABLE I. *Individual patient data and doses of lignocaine. Asterisks denote dose attained before mild toxicity symptoms necessitated curtailment of infusion*

Patient	Diagnosis	Age (yr)	Weight (kg)	Lignocaine dose (mg)		
				Bolus	Infusion	Total
E.H.	Thalamic pain	68	84	300	240	540
H.S.	Post rhizotomy pain	60	60	250	200*	450
P.D.	Arachnoiditis	37	82	240	240	480
B.F.	Trigeminal neuralgia	37	55	200	240	440
D.S.	Phantom pain	53	41	140	180*	320

veloped. Further, all subjects developed intolerable ischaemic pain 15–30 min into the study which necessitated the release of the cuff before the full occlusion time of 1 h had elapsed. A maximum pain score of 100 was then extrapolated for the ischaemic pain intensity until completion of the study.

RESULTS

The concentrations of lignocaine in arterial blood for each patient are presented in table II. Peak values of $5.62 \pm 1.39\,\mu g\,ml^{-1}$ were observed immediately following injection of the $3\text{-mg}\,kg^{-1}$ dose, with a rapid decline during the subsequent infusion. Over this time a plateau concentration was well maintained in each patient with mean values about $1.5\text{–}2.0\,\mu g\,ml^{-1}$ although, as noted in table I, two patients did not receive the maximum infusion dose of 240 mg. Both patients began to develop signs of toxicity, such as drowsiness, slurred speech, or tremors, at which point the infusion of lignocaine was discontinued. No patient showed any major toxicity and the only changes noted on e.c.g. monitoring consisted of a mild ($15\text{–}25\ \text{beat}\,min^{-1}$) increase in heart rate.

The scores of pain intensity for ischaemic and clinical pain are presented in table III. Statistical analyses of these scores using the paired Student's *t* test, showed no difference between the pre-infusion values but at time 0 (immediately on completion of the initial 3-min administration of lignocaine) the clinical pain was diminished to a value of 12 ± 11.6 as against a significantly lesser decrease (36 ± 30.3, $P < 0.01$) for the ischaemic pain. Further, this mild analgesic action on ischaemic pain could not be sustained and the intensity of the pain continued to increase despite the continued infusion of lignocaine, reaching a maximum of 100 in all patients within 15 min. The cuff was released at this time on three patients and at 30 min for the remaining two. In contrast, the severity of clinical pain remained at a level significantly below that of the control during the entire lignocaine infusion. A statistically significant difference in the intensity of pain existed between the ischaemic pain value and the clinical pain value throughout the entire infusion period.

The relationships between the mean values for intensity of ischaemic pain, clinical pain and the mean arterial lignocaine blood concentrations are shown in figure 1. The initial decline in both ischaemic and clinical pain is correlated with arterial lignocaine concentrations in excess of $3\,\mu g\,ml^{-1}$. As the blood lignocaine concentration decreased below $3\,\mu g\,ml^{-1}$, the severity of ischaemic pain increased,

TABLE II. *Individual and mean whole blood lignocaine concentrations taken from arterial samples. In patients H.S. and D.S. the final samples were not drawn as infusions had ceased*

Patient	Control	Time (min)									
		0	1	2	3	5	10	15	30	45	60
E.L.	0	7.75	4.21	2.94	2.57	2.04	1.46	1.45	1.36	1.32	1.23
H.S.	0	3.94	3.26	2.70	2.35	2.36	2.31	2.05	2.07	2.18	—
P.D.	0	5.66	4.50	3.20	2.57	2.13	1.86	1.52	1.50	1.54	1.54
B.F.	0	5.78	2.78	2.45	2.45	2.52	2.21	2.17	2.08	2.03	2.01
D.S.	0	4.98	4.90	3.29	3.05	2.61	1.58	1.71	1.85	3.82	—
Mean		5.62	3.93	2.91	2.59	2.33	1.88	1.78	1.77	2.17	1.59
SD		1.39	0.88	0.34	0.26	0.24	0.37	0.31	0.32	0.98	0.39

TABLE III. *Linear analogue pain scores for both ischaemic and clinical pain in each patient. Control = pre-infusion values, 0 = end of the rapid infusion/beginning slow infusion period and times thereafter are minutes of steady infusion time. Differences in pain intensity were significant at all infusion intervals although the ischaemic pain scores were extrapolated at a 100 value if the preceding two recordings were at that value.* P *values from paired Student's* t *test*

		Time (min)										
Patient	Control	0	1	2	3	5	10	15	30	45	60
Ischaemic pain scores											
E.C.	100	70	70	70	70	100	100	100	100	100	100
H.S.	80	0	0	0	100	100	100	100	100	100	100
P.D.	70	65	70	70	40	90	100	100	100	100	100
B.F.	50	25	25	50	75	80	100	100	100	100	100
D.S.	25	20	0	75	80	80	90	100	100	100	100
Mean	65	36	33	53	73	90	98	100	100	100	100
SD	28.72	30.29	35.25	31.14	21.68	10.00	4.47	0	0	0	0
Clinical pain scores											
E.L.	50	30	30	30	30	30	10	10	5	5	5
H.S.	100	0	0	0	0	0	0	0	0	0	0
P.D.	60	20	0	0	20	70	50	20	55	30	0
B.F.	50	10	10	10	10	10	2	5	2	2	5
D.S.	27	0	0	0	0	0	0	0	1	0	0
Mean	57.4	12	8	8	12	22	12.4	7	12.6	7.4	2
SD	26.72	11.66	13.04	13.04	13.04	29.50	21.42	8.37	23.78	12.80	2.74
P	<0.3	<0.01	<0.05	<0.01	<0.002	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005

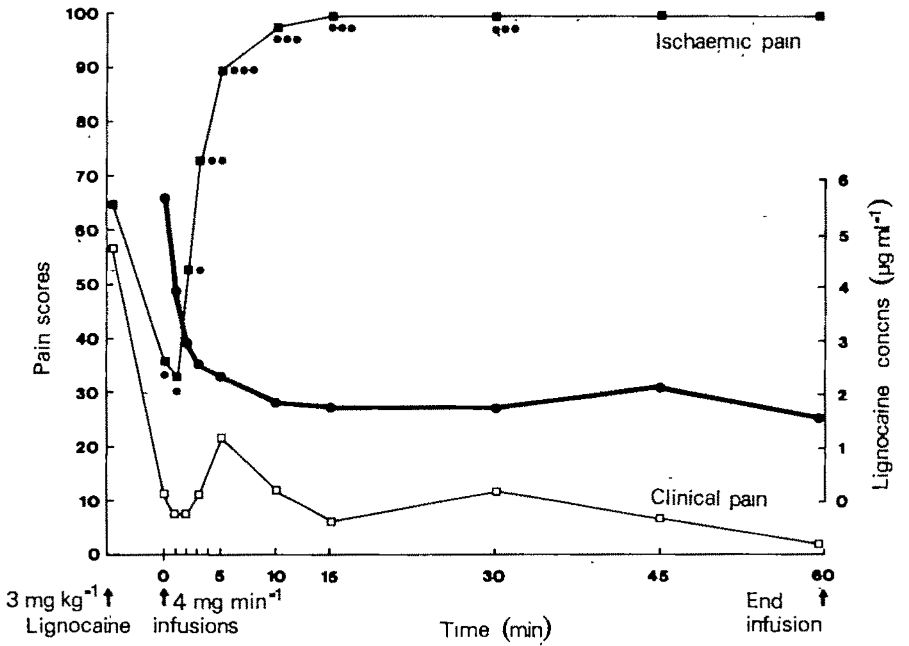

FIG. 1. The effect of lignocaine on clinical (open squares) and experimental pain (closed squares). Graphed mean values are represented for each pain state with mean arterial lignocaine concentrations in the solid line. Following the initial high-dose infusion both pain scores decreased considerably, but the decrease in clinical pain intensity was significantly greater. At a critical concentration of $3\,\mu g\,ml^{-1}$, the analgesic action of lignocaine on experimental pain was lost while that on clinical pain was sustained to values less than $2\,\mu g\,ml^{-1}$. The difference in response was significant ($P<0.0005$) at 5 min and at each determination thereafter.

whereas the severity of clinical pain remained significantly decreased. Two of these five patients showed complete abolition of their pain, two others showed almost complete abolition, whereas one patient showed fluctuation in the intensity of clinical pain. This patient suffered arachnoiditis, having a peripheral nerve injury component to his pain, in distinction to the others who were suffering deafferentation pains.

DISCUSSION

The results of this study are in agreement with reports of others examining the analgesic action of systemic local anaesthetic agents. However, two critical distinctions are apparent in delineating this analgesic action. First, a mild general systemic analgesic effect is evident at blood concentrations greater than 3 μg ml^{-1}, while a more specific and profound effect is provided at much lower concentrations in patients with central or deafferentation types of pain. Thus Rowlingson and colleagues (1980), in examining peripheral experimental pain, found lignocaine to be without effect in concentrations up to 3 μg ml^{-1} while the effectiveness of procaine on central neuralgic disorders was found to be dramatic in reports by Graubard, Robertazzi and Peterson (1948) who used prolonged infusions of the drug as a method of pain therapy for these and other patients. The doses chosen for the administration of lignocaine in this study were taken from those of Harrison (1975) who devised similar regimens to attain rapid steady blood concentrations for treating cardiac arrhythmias. Although the doses were not tailored to the individual patient, the methodology was simplified without compromising the subsequent kinetic profiles over the limited time-course of the study.

As a consequence of these results it appears that chronic pain of the deafferentation type may be more responsive to the analgesic action of lignocaine in concentrations of about 1.5–2.0 μg ml^{-1}, at which concentrations we could not demonstrate any general analgesic action.

Against this hypothesis one could argue that the increasing experimental pain diminished the clinical pain, but the early parallel movement of the two responses in this study favours a common action rather than that of one upon the other. Also the ischaemic pain test (Sternbach et al., 1974), used to measure the intensity of clinical pain, produced no apparent change in the pre-existing pain disorder. Restriction of the access of the drug to the tissues of the occluded limb could also be stated to bias the response in favour of suppression of the clinical pain, but this was the essential point of Rowlingson's paper (Rowlingson et al., 1980) which showed that at the blood concentrations in question, lignocaine had no suppressive effect on peripherally-induced experimental pain.

While any explanation to account for this response is conjectural, part of the action may be the result of a decrease in the rate of neuronal depolarization as occurs in excitable tissues of the heart, or could be from a selective decrease in high frequency impulse transmission as demonstrated by Condouris (1976). Of greater clinical relevance is a recognition that the response to diagnostic blocks in some instances may be as much a result of the systemic activity of the drug, as of the local nerve blocking effect of lignocaine. Such an action would readily explain the discrepancy between effective analgesia of diagnostic blocks and subsequent failure of permanent nerve interruption (Tasker, Orgon and Hawrylyshyn, 1980). Further clinical applications may derive from the use of lignocaine i.v. to assist in the diagnosis of pain disorders or, additionally, such infusions may provide a rational therapeutic alternative to temporary remission of central pain for some patients.

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RESPONSES ANALGESIQUES A LA LIGNOCAINE INTRAVEINEUSE

RESUME

L'effet analgésique de la lignocaïne intraveineuse a été étudié chez cinq sujets souffrant de douleurs spontanées d'origine neurologique de diverses étiologies. La réponse a été comparée à celle obtenue sur une douleur ischémique provoquée concurremment, et initialement de même intensité. Après la perfusion d'une dose élevée de 3 mg kg^{-1}, permettant d'atteindre des concentrations de lignocaïne supérieures à 3 μg ml^{-1}, les deux douleurs diminuent et la douleur spontanée davantage que l'autre, ce de façon statistiquement significative. Après cela, à des doses et des concentrations sanguines plus faibles, la lignocaïne est restée sans effet sur la douleur ischémique, alors qu'elle supprimait presque complètemnet la douleur spontanée chez le même patient. Les résultats suggèrent une divergence dans la spécificité de l'action analgésique de la lignocaïne i.v. selon la naturé du processus causal de la douleur. Les troubles se manifestant comme une déafférentation ou des douleurs neurologiques d'origine centrale semblent affectés favorablement par la lignocaïne i.v., alors que les douleurs d'origine périphérique ne sont pas modifiées par la lignocaïne, sauf à des concentrations sanguines proches des valeurs toxiques.

RESPUESTAS ANALGESICAS A LA LIGNOCAINA INTRAVENOSA

SUMARIO

Se evaluó el efecto analgésico de la lignocaína intravenosa en cinco pacientes con dolor neurálgico clínico de diversas etiologías. La respuesta se comparó con la del dolor isquémico inducido al mismo tiempo, que al principio fue de la misma intensidad. A raiz de una infusión de alta dosis, 3 mg kg^{-1} (las concentraciones de lignocaína fueron superiores a 3 μg ml^{-1}), ambos dolores clínicos disminuyeron hasta un grado significativo. Con posterioridad y con dosis y concentraciones sanguíneas inferiores, la lignocaína no ejerció efecto alguno en el dolor isquémico, pero suprimió casi totalmente el dolor clínico. Los resultados sugieren que la actividad analgésica de la lignocaína intravenosa es específica, según sea la naturaleza del proceso de inducción del dolor. Los desórdenes que se manifiestan como una diferenciación o neuralgias centrales parecen ser afectados favorablemente por la lignocaína intravenosa, mientras que ésta no afecta al dolor de origen periférico, excepto a concentraciones sanguíneas que se acercan a valores tóxicos.

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EFFECT OF DIFFERENT KINDS OF PREMEDICATION ON THE INDUCTION PROPERTIES OF MIDAZOLAM

J. KANTO, S. SJÖVALL AND A. VUORI

SUMMARY

The effects of different premedication (i.m. and i.v.) on the usefulness of midazolam or thiopentone as induction agents for minor surgery was studied in 194 women undergoing either dilatation and curettage or explorative fractionate curettage. Midazolam appeared to produce light sedation which required powerful premedication (i.m. atropine + pethidine and i.v. fentanyl or fentanyl + dehydrobenzperidol) when used as an induction agent for minor surgery. The clinically useful dose of midazolam is about 0.30 mg kg^{-1} i.v. There was greater variability in onset and duration of action among patients receiving midazolam than among those receiving thiopentone. Midazolam caused less respiratory depression, but there were no clinically significant differences between midazolam and thiopentone with respect to cardiovascular variables. Muscular movements were found more often, and postoperative sedation lasted longer in patients receiving midazolam. Midazolam as an induction agent appears more suited for major than for minor surgery.

Midazolam hydrochloride (Ro 21-3981), is a 1,4-benzodiazepine derivative currently being evaluated as an induction agent in anaesthesia. It differs from other benzodiazepines in that it is water-soluble, has a half-life of about 2 h (about one-tenth that of diazepam and flunitrazepam), and does not cause significant thrombophlebitis. In addition, while anterograde amnesia seems to be more marked it is of shorter duration than with other benzodiazepines (Conner et al., 1978; Brown et al., 1979; Reves et al., 1979; Dundee and Wilson, 1980). Midazolam, like other benzodiazepines, effectively maintains haemodynamic and respiratory variables even in poor-risk patients (Forster et al., 1979; Fragen and Caldwell, 1980; Samuelson et al., 1980). Its onset of action is quicker, and there is less individual variation in response than after the administration of diazepam (Reves, Corssen and Holcomb, 1978). In this open study we compared the effect of different premedicants on the onset of action of midazolam hydrochloride, on the maintenance of anaesthesia induced with midazolam hydrochloride, and on recovery from such anaesthesia, for minor gynaecological operations. The results were compared with those produced with thiopentone.

PATIENTS AND METHODS

A total of 194 women participated in this study (table I). All were undergoing either dilatation and curettage or explorative fractionate curettage. Each patient received atropine 0.5 mg and pethidine 50 mg i.m. about 1 h before the surgical intervention. In group 1 (fig. 1), 44 patients received midazolam hydrochloride (Ro 21-3981) as an induction agent in increasing dose (from 0.15 to 0.5 mg kg^{-1} i.v.) over 30 s to determine the clinically useful dose for minor surgery. If there were involuntary muscular movements or other disturbing sequelae, thiopentone was given i.v., in addition, in increments of 50 mg. The results in group 1 were compared with those produced in 30 patients receiving thiopentone sufficient to affect loss of the eye lash reflex. In group 2, fentanyl 50 µg was injected i.v. 1 min before the beginning of anaesthesia induced either with midazolam 0.30 ± 0.01 mg kg^{-1} ($n = 30$) or thiopentone 6.6 ± 0.3 mg kg^{-1} 6.0 ± 0.3 mg kg^{-1} ($n = 30$) in 30 s. In group 3, the patients received both fentanyl 50 µg and dehydrobenzperidol 2.5 mg 1 min before the induction of anaesthesia with either midazolam 0.37 ± 0.02 mg kg^{-1} ($n = 30$) or 6.6 ± 0.3 mg kg^{-1} thiopentone ($n = 30$). Anaesthesia was supplemented with 70% nitrous oxide in oxygen in all patients. No i.v. infusion was used.

The following were recorded by the anaesthetist during and after anaesthesia: time of spontaneous closing of the eyes after commencing i.v. injection of midazolam or thiopentone; disappearance of the

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TABLE I. *Characteristics of the patients (mean ± SEM)*

	Group 1		Group 2		Group 3	
	Midazolam	Thiopentone	Midazolam	Thiopentone	Midazolam	Thiopentone
Age (yr)	39.8 ± 1.9	43.5 ± 2.2	39.8 ± 2.7	36.5 ± 2.2	35.0 ± 2.3	35.6 ± 2.2
Weight (kg)	64.2 ± 1.6	66.7 ± 1.9	64.8 ± 1.7	64.7 ± 1.7	63.0 ± 1.4	62.4 ± 1.7
Height (cm)	163.3 ± 0.9	162.4 ± 1.1	164.6 ± 1.2	163.9 ± 0.9	164.1 ± 1.0	163.3 ± 1.0
ASA class 1	$n = 37$	$n = 24$	$n = 28$	$n = 27$	$n = 29$	$n = 28$
ASA class 2	$n = 7$	$n = 6$	$n = 2$	$n = 3$	$n = 1$	$n = 2$

eyelash reflex; respiratory rate; appearance and duration of apnoea (absence of respiration for longer than 10 s); heart rate and arterial pressure; hiccup, cough, involuntary muscular movements and related unwanted effects during surgical intervention; sleeping time; state of vigilance in the recovery room (about 30 min): alert, fairly alert or sedated; lower abdominal muscular relaxation during gynaecological examination (gynaecologist): good, fair or poor.

In addition, following anaesthesia in group 3, the following were recorded by nurses in the ward: degree of sedation when coming to the ward: alert, fairly alert or sedated; time for return to full consciousness (patient able to take care of herself): <1 h, 1–3 h, >3 h; postoperative nausea and vomiting; psychic state in the evening: clear, moderately clear or tired; patients' opinion of the anaesthetic, when asked by the nurse on the following day: good, fair or unacceptable.

Statistical analyses of the results were carried out by Student's *t* test (parametric data) or by the χ^2-test (non-parametric data).

RESULTS

The ability of midazolam to induce sleep was slower in onset, with a wider interindividual variability than that of thiopentone (fig. 1). Three patients (two receiving diazepam and one carbamazepine therapy) were excluded from the study, because they were

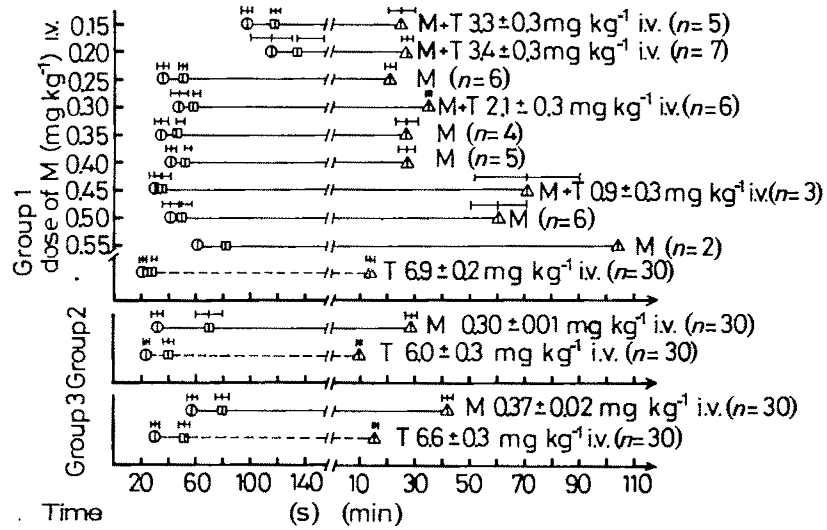

FIG. 1. Effect of increasing doses of midazolam (M) i.v. on time to spontaneous closing of the eyes (○), disappearance of palpebral reflex (□), and duration of sleep (△) (mean ± SEM). In group 1, a fixed dose of midazolam was injected i.v. in 30 s and bolus doses (50 mg) of thiopentone (T) given if needed. In group 2, fentanyl 50 µg and in group 3, fentanyl 50 µg with dehydrobenzperidol 2.5 mg was injected i.v. 1 min before the administration of midazolam over 30 s (according to the response of the patient). Results in each of the three patient groups were compared with those produced by thiopentone 5 mg kg^{-1} i.v. in 30 s. As can be seen, many patients fell asleep less than 30 s after commencing the administration of thiopentone, and some additional doses were needed later.

still awake 5 min after the administration of up to 0.5 mg kg^{-1} of midazolam. Each dose of midazolam, or of midazolam plus a small dose of thiopentone caused a sleeping time distinctly longer than the usual dose of thiopentone. This difference was significant in each of the three groups of patients ($P<0.001$).

In contrast, respiratory depression after the administration of thiopentone was clearly more marked than after the administration of midazolam (fig. 2). In addition, apnoea lasting more than 10 s was recorded in 12–67% of patients in whom anaesthesia was induced with thiopentone, but in only 2–10% of those receiving midazolam. In both instances, the previous administration of fentanyl and, more expecially, fentanyl with dehydrobenzperidol increased the frequency of apnoea. The mean total period of apnoea varied between 36.6 and 59.8 s in thiopentone-induced patients and between 14.2 and 17.8 s in patients receiving midazolam ($P<0.001$ in each of the three groups of patients).

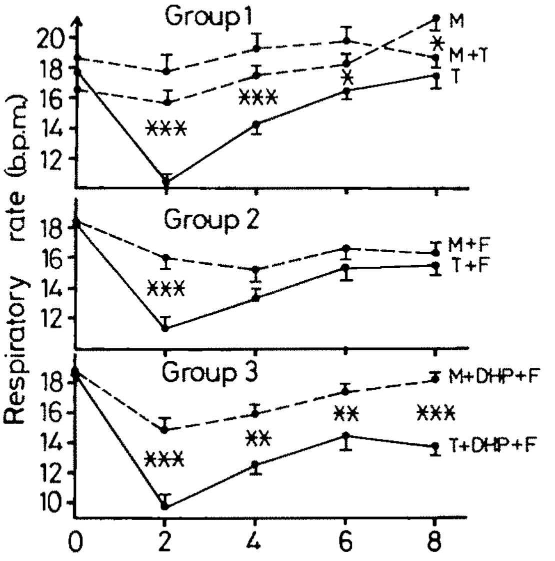

FIG. 2. In group 1, the respiratory depression with thiopentone (T) was more marked than that produced by midazolam (M) or by midazolam plus a small dose of thiopentone (M + T). In group 1 (only atropine 0.5 mg i.m. + pethidine 50 mg i.m. premedication) midazolam or M + T did not significantly change the respiratory rate, but in group 2 (atropine i.m. + pethidine premedication + fentanyl 50 µg (F) i.v.) and group 3 (atropine i.m. + pethidine premedication + fentanyl 50 µg i.v. + dehydrobenzperidol (DHP) 2.5 mg i.v.) a significant decrease in respiratory rate was observed after the administration of midazolam (P values at 2 and 4 min $<0.01-0.001$). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

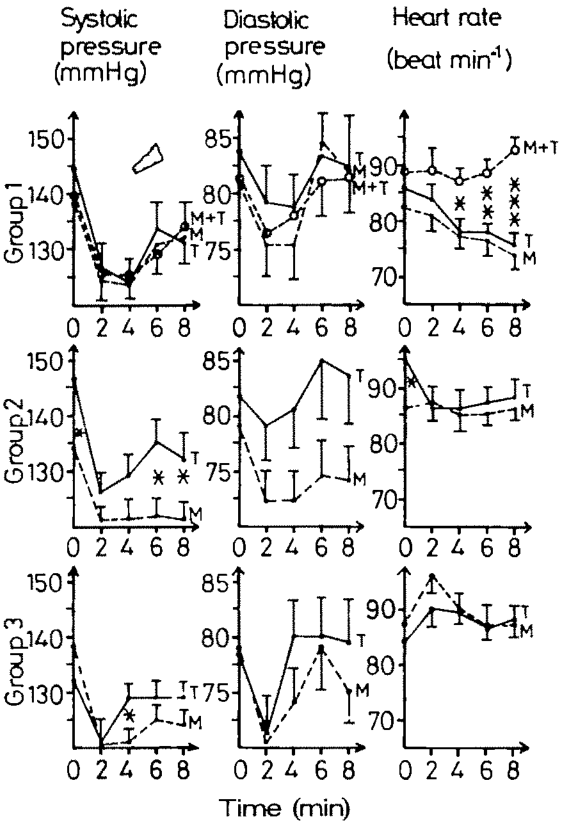

FIG. 3. There were no clinically significant differences in cardiovascular parameters between midazolam (M) and thiopentone (T). The faster heart rates in M + T patients (group 1) were caused by the small bolus doses of thiopentone 50 mg which were injected only if the action of midazolam was unacceptable.

There were no clinically-relevant differences in cardiovascular indices between patients receiving midazolam and those receiving thiopentone (fig. 3). In group 1, the significantly higher heart rates in patients receiving midazolam (plus a small additional dose of thiopentone) were apparently a result of the design of the study: thiopentone was given only when the effect of midazolam had worn off.

Hiccup, cough, disturbing involuntary muscular movements and related unwanted effects were recorded more often after midazolam (group 1: 57% v. 37%; group 2: 46% v. 23%; group 3: 43% v. 10%). Lower abdominal relaxation, as assessed by the gynaecologist, was similar after both induction agents.

TABLE II. *Sedation caused by midazolam (M) and thiopentone (T), assessed in the recovery room*

	Group 1			Group 2			Group 3		
	T	M	*P*	T	M	*P*	T	M	*P*
Alert	20	15		22	4		7	0	
Fairly alert	7	8	<0.01	6	9	<0.001	15	8	<0.001
Sedated	3	21		2	17		8	22	

In the recovery room, patients in whom anaesthesia was induced with midazolam were clearly more sedated than those induced with thiopentone (table II). The opinions formed by the nurses when the patients returned to the ward, were similar (assessed in group 3 only). However, as regards time for return to full consciousness, postoperative nausea and vomiting, psychological state in the evening and patients' opinion of anaesthesia, there were no significant differences between the patients receiving midazolam or thiopentone (group 3 only).

DISCUSSION

We found midazolam to be a mild hypnotic which requires powerful premedication when used alone as an anaesthetic agent for minor surgery. After the administration of fentanyl or fentanyl plus dehydrobenzperidol anaesthesia could be induced easily. Similar experiences have been obtained in patients undergoing major surgery (to be published). Generally, a distinctly wider interindividual variability, both in onset and duration of action, was found with midazolam as compared with thiopentone. The slow onset of anaesthesia was assessed as subjectively pleasant by some patients who had received thiopentone on a previous occasion. However, the longest of the induction times and durations of action observed in this study are clinically unacceptable in minor surgery. Thus, this new benzodiazepine derivative appears to be useful either as an induction agent for major surgery or as a general basal sedative before surgery.

The sedative effect lasted longer after operation in the patients receiving midazolam. This is a drawback in hospitals like ours where there are only a few recovery rooms. On the other hand, this property of an induction agent appears to be subjectively pleasant and decreases the amount of analgesic needed following surgery. After the return to the ward, the difference in the sedative effect disappeared in a short time and the subjective and objective psychic state was, thereafter, comparable in patients in whom anaesthesia was induced with midazolam or thiopentone.

The dose of midazolam which is clinically useful in minor surgery appears to be greater than that suggested by the manufacturer (0.15 mg kg^{-1}). In this respect, we agree with Dundee and Gamble (1981): at least 0.30 mg kg^{-1} i.v. should be administered to induce clinically acceptable anaesthesia.

In our relatively healthy patients there were no clinically significant differences in cardiovascular variables between patients receiving midazolam or thiopentone. In contrast, midazolam caused clearly less respiratory sequelae, being comparable to diazepam in this respect (Fragen, Gahl and Caldwell, 1978). On account of these effects on respiration and circulation, midazolam has been recommended for poor-risk patients (Reves and Samuelson, 1979).

Although benzodiazepine derivatives have a central muscle relaxant effect there was no difference in this respect between midazolam and thiopentone. The reason may lie in the deeper anaesthesia caused by the barbiturate. This is further supported by the greater prevalence of disturbing muscular movements during surgical intervention in the patients receiving midazolam.

In conclusion, midazolam appears to be a mild hypnotic which needs relatively strong premedication to induce clinically acceptable anaesthesia in minor surgery. It is more suitable for major than for minor surgery. In comparison with our earlier studies with diazepam (Kanto and Iisalo, 1973) and flunitrazepam (Kangas, Kanto and Pakkanen, 1981; Kanto et al., 1981) the main novel property of midazolam is its distinctly shorter duration of action. However, it is not comparable to thiopentone in this respect. Our results are similar to other preliminary experiences with midazolam (Fragen, Gahl and Caldwell, 1978; Reves, Corssen and Holcomb, 1978; Fragen and Caldwell, 1980).

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EFFET DE DIFFERENTES SORTES DE PREMEDICATION SUR LES PROPRIETES D'INDUCTION DU MIDAZOLAM

RESUME

Nous avons étudié les effets de différentes prémédications i.m. et i.v. sur l'utilité du midazolam ou du thiopental comme agents d'induction pour des actes de chirurgie mineure chez 194 femmes subissant soit une dilatation et un curetage, soit un curetage biopsique fractionné. Le midazolam est apparu comme induisant une sédation légère, qui nécessitait une prémédication puissante (atropine + péthidine i.m. et fentanyl i.v. ou fentanyl + dropéridol) lorsqu'on l'utilisait comme agent d'induction pour des actes de chirurgie mineure. La dose de midazolam nécassaire en clinique est d'environ 0,30 mg kg^{-1} i.v. Les variations de délai d'induction et de durée d'action sont plus importantes chez les patientes qui reçoivent du midazolam. Le midazolam apparait convenir davantage comme agent d'induction pour les actes de chirurgie majeure que pour ceux de chirurgie mineure.

AUSWIRKUNG VON VERSCHIEDENEN PRÄMEDIKATIONEN AUF DIE EIGENSCHAFTEN VON MIDAZOLAM ALS EINLEITUNGSMITTEL

ZUSAMMENFASSUNG

Der Einfluß verschiedener Prämedikationen – i.m. u. i.v. – bei der Verwendung von Midazolam oder Thiopental zur Einleitung für Kurzeingriffe wurde an 194 Frauen studiert, die sich einer Dilatation mit Curettage oder einer diagnostischen Curettage unterziehen mußten. Midazolam schien nur eine leichte Sedierung zu bewirken, die deshalb eine starke Prämedikation erforderlich machte (i.m. Atropin + Pethidin und i.v. Fentanyl oder Fentanyl + Dehydrobenzperidol), wenn es als Einleitungsmittel für Kurzeingriffe verwendet wurde. Bei Midazolam ist eine Dosis von 0,3 mg kg^{-1} erforderlich. Die Unterschiede in bezug auf Einsetzen und Dauer der Wirkung waren bei Midazolam größer als bei Thiopental. Midazolam rief weniger Atemdepression hervor, aber zwischen Midazolam und Thiopental bestanden keine signifikanten Unterschiede in der Kreislaufwirkung. Muskelbewegungen waren häufiger und die postoperative Sedierung dauerte länger bei Patienten, die Midazolam erhalten hatten. Midazolam scheint besser als Einleitungsmittel für große Operationen als für Kurzeingriffe geeignet zu sein.

EFECTO DE DIFERENTES CLASES DE PREMEDICACION EN LAS PROPIEDADES DE INDUCCION DEL MIDAZOLAM

SUMARIO

Se estudiaron los efectos de diferente medicación (intramuscular e intravenosa) en lo tocante a la utilidad del midazolam o de la tiopentona como agentes inductores conducentes a cirujía menor, en 194 mujeres sometidas a dilatación y curetaje o bien curetaje fraccional y explorativo. El midazolam pareció producir una ligera sedación, que necesitó una poderosa premedicación (intramuscular atropina + petidina y intravenoso fentanilo o fentanilo + deshidrobenzperidol) cuando se usó como un agente de inducción para cirujía menor. La dosis de midazolam clínicamente útil es de unos 0,30 mg kg^{-1} intravenosos. Hubo una mayor variabilidad en el comienzo de la actividad y en su duración en los pacientes que recibieron midazolam que entre los que recibieron tiopentona. El midazolam causó menos depresión respiratoria, pero no hubo diferencias de significación clínica entre el midazolam y la tiopentona con respecto a las variables cardiovasculares. Los pacientes que recibieron midazolam presentaron movimientos musculares, con más frecuencia y la sedación postoperativa fue más duradera en estos pacientes. Elmidazolam, como agente de inducción, parece ser más adecuado para intervenciones mayores que para las menores.

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BINDING OF TUBOCURARINE, FAZADINIUM, PANCURONIUM AND ORG NC 45 TO SERUM PROTEINS IN NORMAL MAN AND IN PATIENTS WITH CIRRHOSIS

P. DUVALDESTIN AND D. HENZEL

SUMMARY

The protein binding of four non-depolarizing neuromuscular blocking drugs—tubocurarine, fazadinium, pancuronium and Org NC45—was measured, in serum from normal patients and from patients with cirrhosis of the liver, by an ultracentrifugation method. The fraction bound to serum protein in normal patients was 56% for tubocurarine, 51% for fazadinium, 29% for pancuronium and 30% for Org NC45. In patients with cirrhosis, the protein binding of the four drugs was similar to that obtained in the normal patients.

Based on pharmacokinetic principles the protein-free concentration of neuromuscular blocking drugs is that which is pharmacologically active. However, in most pharmacodynamic studies, the effect of the binding to plasma proteins is ignored and the computed active concentration in the perisynaptic space is apparent rather than real (Hull, English and Sibbald, 1980). Although several studies have been performed on the protein binding of neuromuscular blocking drugs in human plasma the results have been controversial. The binding of pancuronium varies from 13% (Wood, Stone and Wood, 1980) to 80% (Thompson, 1976), dimethyl-tubocurarine from 35% (Meijer et al., 1979) to 70% (Dal Santo, 1964) and tubocurarine from 30% (Cohen, Brewer and Smith, 1967) to 50% (Meijer et al., 1979). These varied results can be explained partly by differences in the experimental method or because the range of concentration studied often exceeded the clinical range. Problems with the different methods used for the estimation of protein binding involve primarily the cellulose membrane since at low concentrations neuromuscular blockers may bind to the membrane. The ultracentrifugation technique avoids these problems in that it is rapid and there is no membrane. In the present work, the protein binding of four non-depolarizing neuromuscular blockers—tubocurarine, fazadinium, pancuronium and Org NC45—was studied at concentrations obtained in anaesthetic practice. Two different methods of estimation were used: equilibrium dialysis and ultracentrifugation. This study was carried out on healthy patients who were compared with patients with cirrhosis. The latter are thought to have an increase in their capacity to bind non-depolarizing blockers (Stovner, Theodorsen and Bjelke, 1971) and a relative resistance to their effects (Dundee and Gray, 1953).

SUBJECTS AND METHODS

Venous blood samples (20 ml) were obtained from normal healthy patients and from patients with cirrhosis of the liver. Informed consent was obtained. The diagnosis of cirrhosis had been established in those patients by previous histological examination of a liver biopsy. The blood samples were allowed to clot and then centrifuged at 3500 rev min^{-1} for 15 min. The serum was kept at 4°C until protein binding was studied. Binding to albumin was studied using human pooled albumin (Centre National de Transfusion Sanguine, Paris, France). Protein binding was measured in the first part of the study by the ultracentrifugation method standardized by Peterson and colleagues (1977). The neuromuscular blocking drug was mixed with the human serum. Tritium labelled tubocurarine (New England Nuclear Corporation, Boston, Massachusetts) was purified according to the method of Cohen, Brewer and Smith (1967). The study was undertaken with concentrations of 1 μg ml^{-1} for tubocurarine labelled with tritium 1.5 nCi ml^{-1}; 1.5 μg ml^{-1} for fazadinium and 0.3 μg ml^{-1} for pancuronium and Org NC 45. These concentrations are

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achieved normally in anaesthetic practice and correspond to a depression of the twitch response of between 90 and 100%. The pH of the serum was brought to 7.2–7.4 unit with sodium bicarbonate. Centrifugation was undertaken in centrifuge cells (at 4°C) for 2 h at 295 000 *g* with a Beckman 65 fixed angle rotor. Five samples, including the initial sample were taken from the tube at 1-cm intervals and the concentrations of protein and drug determined. In the Org NC45 experiments, the samples which were obtained after ultracentrifugation were immediately acidified at pH 6, to prevent spontaneous hydrolysis of the compound at pH 7.4. The concentration of the neuromuscular blocker was plotted against the concentration of protein using linear regression analysis. The amount of free drug was determined by extrapolating to zero protein.

Protein binding of pancuronium and fazadinium was determined by equilibrium dialysis. One millilitre of serum in Visking cellophane bags was dialysed against a freshly prepared pH 7.4 phosphate (0.0175 mol litre^{-1}) buffer. The concentrations of pancuronium and fazadinium in the buffer were of 0.3 μg ml^{-1} and 1.5 μg ml^{-1} respectively. The time used for equilibration was 18 h. After equilibrium the drug concentration was determined in both the cellophane bag and the phosphate buffer.

The concentration of tubocurarine was determined by assaying the radioactivity by liquid scintillation counting. Fazadinium was determined by a spectrofluorimetric method (Pastorino, 1978). The precision (relative standard deviation, percent) of the assay determined by eight-fold processing of fazadinium 1 μg added to 1 ml of human plasma was 2%. Pancuronium and Org NC45 were measured using a minor modification of the Rose Bengale spectrofluorimetric method (Kersten, Meijer and Agoston, 1973). The precision of the assay determined by six-fold processing of 250 ng of pancuronium or Org NC45 added to 1 ml of human plasma was 5.0% and 4.5% for pancuronium and Org NC45 respectively. The total protein concentration was determined by the method of Lowry and others (1951). The Mann–Whitney test was used for comparing the groups (Siegel, 1956).

RESULTS

A typical example of the method of determination of the protein binding of pancuronium by the ultracentrifugation method is presented in figure 1.

The percentages of the four drugs bound to serum protein in the normal patients and in the patients with cirrhosis are depicted in table I. The fraction bound to serum protein was relatively small: 56% for tubocurarine, 51% for fazadinium, 29% for pancuronium and 30% for Org NC45. There were no marked interindividual differences in the bound fraction of these four drugs. In patients with cirrhosis, the degree of protein binding of tubocurarine, fazadinium, pancuronium and Org NC45 was similar to that obtained in the normal patients (table I). The degree of protein binding determined by equilibrium dialysis was 53 ± 2% for fazadinium and 20 ± 8% for pancuronium and was not significantly different from the value determined by ultracentrifugation. Protein binding was studied at different concentrations of 0.5, 1.0, 1.5 and 2 μg ml^{-1} for tubocurarine and of 1.5 and 3 μg ml^{-1} for fazadinium. The extent of binding of tubocurarine and of fazadinium remained constant over the range of concentrations studied. In human serum albumin solution (45 g litre^{-1}), 53% of tubocurarine and 49% of fazadinium were bound. No sedimentation of any of the neuromuscular blocking drugs was observed after ultracentrifugation of the protein-free serum ultrafiltrate containing the drug. Org NC45 may undergo a spontaneous breakdown in aqueous solution and, therefore, its stability was tested over a period of time equivalent to that required to determine its extent of protein binding. During the duration of the ultracentrifugation no spontaneous breakdown of Org NC45 was observed. The concentration found in an aliquot of

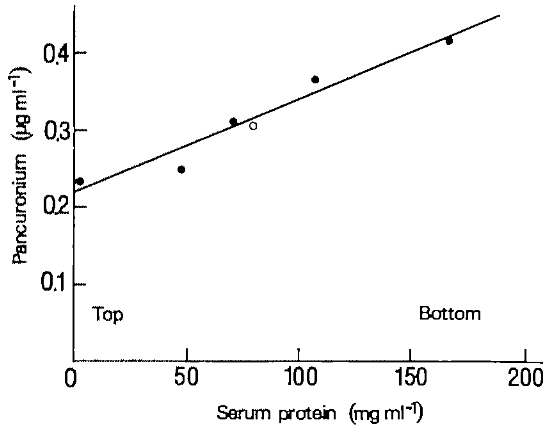

FIG. 1. Pancuronium and protein concentrations in fractions of human serum after ultracentrifugation. Five samples (●) and the starting sample (○) were taken from the top to the bottom of the cell. The protein-free concentration corresponds to the intercept with the origin.

TABLE I. *Serum protein binding as percent of total concentration of neuromuscular blocking drugs in normal patients and in patients with cirrhosis (mean values ± SD).* n = *Number of serum samples studied by ultracentrifugation*

	Tubocurarine 1.0 µg ml^{-1}	Fazadinium 1.5 µg ml^{-1}	Pancuronium 0.3 µg ml^{-1}	Org NC 45 0.3 µg ml^{-1}
Normal	56±9 (n=7)	51±5 (n=6)	29±9 (n=8)	30±9 (n=6)
Cirrhosis	44±9 (n=3)	57±7 (n=5)	38±7 (n=4)	24±8 (n=5)

serum kept at 4°C during the 4 h of the procedure averaged 0.29 ± 0.02 µg ml^{-1} instead of a theoretical value of 0.30 µg ml^{-1} of Org NC 45.

DISCUSSION

This study indicates that the binding of neuromuscular blocking drugs to serum proteins is relatively small in comparison with many other drugs used in anaesthetic practice, the protein binding of which often exceeds 75%. Our results agree with recent studies for tubocurarine in which the bound fraction was estimated as 42% (Meijer et al., 1979). However, our results with pancuronium protein binding are in complete disagreement with those of Thompson (1976) who reported high *in vitro* binding in isolated protein solutions and calculated that 87% of pancuronium would be bound at clinical concentrations. However, the concentrations reported by Thompson (1976) of 1–2 µg ml^{-1}, were markedly greater than the concentrations observed in anaesthetic practice and in our study. In addition, the study of binding in isolated protein preparations probably does not reflect physiological changes in human plasma protein binding. A value of 20% for the protein-bound fraction was found by Waser (1973) in mice serum whereas more recently a value of 13% was obtained for pancuronium in man using the equilibration dialysis technique (Wood, Stone and Wood, 1980). Similar values for the protein binding of fazadinium and pancuronium were observed, using the ultracentrifugation or the equilibrium dialysis method, thus suggesting that both methods are valid. The extent of binding of tubocurarine and fazadinium to albumin was the same as to whole serum, suggesting that most of the binding occurs with albumin. The total concentration of a non-depolarizing drug is often considered to be the active concentration present in the extracellular fluids. In fact, this value should be halved for tubocurarine and fazadinium whereas, for pancuronium and Org NC 45, the error is less important when the total concentration is confused with free concentration. The fraction filtered through the kidneys should be less for tubocurarine than for pancuronium according to their respective degrees of protein binding. This may provide an explanation for the different rates of elimination, pancuronium, with a elimination half-life of 108–147 min (Agoston et al., 1973) being more rapidly eliminated from the plasma than tubocurarine, the elimination half-life of which ranges from 231 min (Miller et al., 1977) to 346 min (Meijer et al., 1979). The factors which contribute to the rapid eliminations of fazadinium and Org NC 45 are not completely elucidated and the influence of protein binding upon their pharmacokinetics is difficult to delineate.

A higher degree of binding to plasma protein and especially to gamma-globulins was suggested to explain the resistance to tubocurarine in patients with cirrhosis. This study clearly demonstrates that there is no increase in the protein-bound fraction of the neuromuscular blockers in patients with cirrhosis and confirms an earlier study of Ghoneim and colleagues (1973) who found no significant difference in the proportions of tubocurarine bound to plasma proteins in healthy patients as compared with patients with hepatic disease. In addition, an extensive binding to gamma-globulins appears unlikely since most of the binding occurs with albumin. The increase in the volume of distribution as shown for pancuronium (Duvaldestin et al., 1978) and fazadinium (Duvaldestin et al., 1980) could also be a possible explanation for the resistance to neuromuscular blockers noted in patients with cirrhosis.

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LIAISON DE LA TUBOCURARINE, DU FAZADINIUM, DU PANCURONIUM ET DE L'ORG NC45 AUX PROTEINES SERIQUES CHEZ L'HOMME NORMAL ET CHEZ LE CIRRHOTIQUE

RESUME

Nous avons mesuré la liaison protéique de quatre curares non dépolarisants: la tubocurarine, le fazadinium, le pancuronium et l'Org NC45, dans le sérum de sujets normaux et de sujets atteints de cirrhose du foie, par une méthode d'ultracentrifugation. Chez les sujets normaux, la fraction liée aux protéines était de 56% pour la tubocurarine, de 51% pour le fazadinium, de 29% pour le pancuronium et de 30% pour l'Org NC45. Chez les cirrhotiques, la liaison protéique des quatre agents était la même que chez les sujets normaux.

DIE PROTEINBINDUNG VON TUBOCURARIN, FAZADINIUM, PANCURONIUM UND ORG NC45 BEI GESUNDEN MENSCHEN UND BEI PATIENTEN MIT LEBERZIRRHOSE

ZUSAMMENFASSUNG

Die Proteinbindung der vier nichtdepolarisierenden neuromuskulären Blocker Tubocurarin, Fazadinium, Pancuronium und Org NC45 wurde im Serum von normalen Patienten und von Patienten mit Leberzirrhose mit einer Ultrazentrifugationsmethode gemessen. Bei normalen Patienten betrug die an das Serumprotein gebundene Fraktion 56% für Tubocurarin, 51% für Fazadinium, 29% für Pancuronium und 30% für Org NC45. Bei den Patienten mit Leberzirrhose war die Proteinbindung der vier Muskelrelaxantien ähnlich wie bei Normalpatienten.

UNION DE LA TUBOCURANINA, EL FAZADINIO, EL PACURONIO Y EL ORG NC45 A LAS PROTEINAS DEL SUERO EN EL HOMBRE SANO Y EN PACIENTES CON CIRROSIS

SUMARIO

Se midió la unión a las proteínas de cuatro drogas de bloqueo neuromuscular no-despolarizante; la tubocurarina, el fazadinio, el pancuronio y el Org NC45; en lo tocante a las proteínas del suero procedente de pacientes sanos y de pacientes con cirrosis del hígado mediante un método de ultracentrifugación. La fracción unida a la proteína del suero en los pacientes sanos fue del 56% para la tubocuranina, 51% para el fazadinio, 29% para el pancuronio y 30% para el Org NC45. En aquellos pacientes con cirrosis la unión de las cuatro drogas a las proteínas fue similar a la obtenida en los pacientes sanos.

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EFFECT OF PHENTOLAMINE ON THE METABOLIC RESPONSE TO GYNAECOLOGICAL SURGERY

E. S. WALSH, J. L. PATERSON, K. MASHITER AND G. M. HALL

SUMMARY

The effect of the infusion of phentolamine 0.5 mg min^{-1} on the metabolic response to gynaecological surgery was investigated. In comparison with a control group of patients, phentolamine was associated with a significant increase in plasma insulin concentration after 30 and 60 min of surgery. The glycaemic response to surgery was decreased by α-adrenergic blockade, but this was only significant after 120 min of surgery. The hypotension produced by the administration of phentolamine was well tolerated.

The use of drugs with α-adrenergic blocking properties, such as the neuroleptic compounds droperidol and chlorpromazine, is common in anaesthetic practice. In addition, agents such as phentolamine are often used for the short-term control of hypertension during anaesthesia. The cardiovascular effects of α-adrenergic blocking drugs are well known, but little attention has been given to the metabolic consequences of the administration of such agents during surgery. The purpose of the present study, therefore, was to examine the effects of a phentolamine infusion on the metabolic and endocrine response to gynaecological surgery.

METHODS

Twenty healthy women, admitted for Fallopian tubal surgery, were investigated. They were allocated randomly to receive either an infusion of phentolamine 0.5 mg min^{-1} or an equivalent volume of 0.9% sodium chloride solution. The nature of the study and the potential hazards were explained to all patients before consent was obtained. The study was approved by the ethics committee of Hammersmith Hospital.

All patients were premedicated with papaveretum 15 mg and hyoscine 0.3 mg i.m. 90 min before surgery. On arrival in the anaesthetic room the duration of starvation before operation was determined and a central venous catheter was inserted percutaneously from an antecubital fossa vein to permit blood sampling and the administration of i.v. fluids. After the patient had rested for 10 min a control blood sample was collected and heart rate, arterial pressure and aural temperature measured. An infusion of either phentolamine 0.5 mg min^{-1} or an equivalent volume of 0.9% sodium chloride solution was started in the contralateral arm and maintained for the duration of the experiment. Fifteen minutes after the start of the infusion another blood sample was collected and the physiological measurements repeated.

Anaesthesia was then induced with thiopentone, the trachea was intubated following the administration of pancuronium and the lungs ventilated with 70% nitrous oxide in oxygen supplemented with 0.5% halothane. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.0–4.5% (Vickers, Datex). Sodium chloride solution 0.9% was infused during surgery at a rate of 6 ml kg^{-1} h^{-1}. Measured blood loss did not exceed 150 ml.

Blood samples were collected at 30-min intervals during surgery and were analysed for glucose, glycerol, lactate and alanine by methods described previously (Hall et al., 1980). Plasma insulin values were determined by radioimmunoassay (Cooper et al., 1980). The concentrations of each metabolite and insulin were estimated in duplicate and the coefficients of variation were: glucose 2.7%, lactate 2.9%, glycerol 4.0%, alanine 4.9% and insulin 5.0%. At the same time as the blood sample was collected the heart rate, arterial pressure and aural temperature were recorded (Holdcroft, Hall and Cooper, 1979).

On the 4th day after operation the skinfold thick-

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TABLE I. *Details (mean ± SEM) of the two groups of patients*

	Saline ($n = 10$)	Phentolamine ($n = 10$)
Age (yr)	32.2±2.0	30.0±1.5
Wt (kg)	60.6±2.9	60.4±2.8
Body fat (%)	31.4±2.0	34.2±1.7
Duration of starvation (h)	16.5±0.9	14.4±0.8

nesses of the patient were measured and the percentage of fat to body weight calculated (Durnin and Rahaman, 1974).

The results are expressed as mean values (± SEM). A two-way analysis of variance was used in both groups to determine the presence of a significant change in mean values with time. A hierarchical two-way analysis of variance was used to assess the significance of any difference in mean values between the two groups.

RESULTS

Details of the patients studied are shown in table I. There was no significant difference between the two groups of patients.

The changes in metabolites, haematocrit and aural temperature are shown in table II. There was a significant increase in blood glucose from 3.70 to 4.52 mmol litre^{-1} ($P < 0.05$) after 60 min of surgery in the control group of patients and the hyperglycaemia persisted for the duration of surgery. In the phentolamine patients, blood glucose increased significantly ($P < 0.05$) only after 30 min of surgery and the glycaemic response was significantly less than the control group after 120 min ($P < 0.05$). Blood lactate increased significantly ($P < 0.05$) after 90 and 120 min of surgery in both groups of patients. There was no significant change in either blood alanine or plasma glycerol concentrations during the study, although the plasma glycerol value in the phentolamine patients was increased significantly ($P < 0.05$) compared with the control group after

TABLE II. *Mean (± SEM) concentrations of substrates, haematocrit and temperature at the following times: S1 = control, S2 = 15 min after saline or phentolamine, S3, S4, S5 and S6 = 30, 60, 90 and 120 min after commencement of surgery respectively. Significance of difference of means from S1 shown by *P < 0.05, **P < 0.01 and ***P < 0.001. Difference between groups for each variable shown in final column. n.s. = not significant*

	S1	S2	S3	S4	S5	S6	Phentol. *v.* saline
Glucose (mmol litre^{-1})							
Control	3.70±0.18	3.83±0.20	4.23±0.23	4.52±0.29*	4.66±0.29*	5.20±0.26**	$P < 0.05$
Phentolamine	3.70±0.18	3.92±0.18	4.38±0.20*	4.13±0.26	4.24±0.21	4.32±0.28	S6
Lactate (mmol litre^{-1})							
Control	0.97±0.24	1.01±0.19	1.06±0.15	1.23±0.16	1.28±0.16*	1.49±0.15*	n.s.
Phentolamine	0.93±0.15	0.78±0.10	0.95±0.07	1.09±0.09	1.17±0.09*	1.17±0.11*	
Alanine (μmol litre^{-1})							
Control	188±27	196±28	144±12	141±22	153±22	148±21	n.s.
Phentolamine	147±20	134±13	134±21	130±19	137±12	172±22	
Glycerol (μmol litre^{-1})							
Control	144±13	123±21	214±39	187±22	184±19	170±22	$P < 0.05$
Phentolamine	170±23	199±24	200±25	184±20	203±10	209±13	S2
Temperature (°C)							
Control	36.0±0.1	35.8±0.1	35.6±0.1**	35.5±0.1***	35.5±0.1***	35.4±0.2***	n.s.
Phentolamine	35.9±0.1	35.8±0.1	35.4±0.1**	35.3±0.2***	35.2±0.2***	35.1±0.2***	
Haematocrit (%)							
Control	39.8±0.5	39.4±0.4	38.8±0.3*	38.0±0.5**	37.0±0.3***	36.3±0.3***	$P < 0.05$
Phentolamine	41.5±0.4	40.5±0.4	39.2±0.4**	38.8±0.5***	37.8±0.4***	37.5±0.4***	S1

15 min of phentolamine. The haematocrit decreased significantly to 36.3% ($P < 0.001$) in the control group and to 37.5% ($P < 0.001$) in the phentolamine patients after 120 min of surgery. The aural temperature decreased to 35.1°C ($P < 0.001$) at the end of the study in the phentolamine patients, but this was not significantly different from the 35.4 °C ($P < 0.001$) in the control patients.

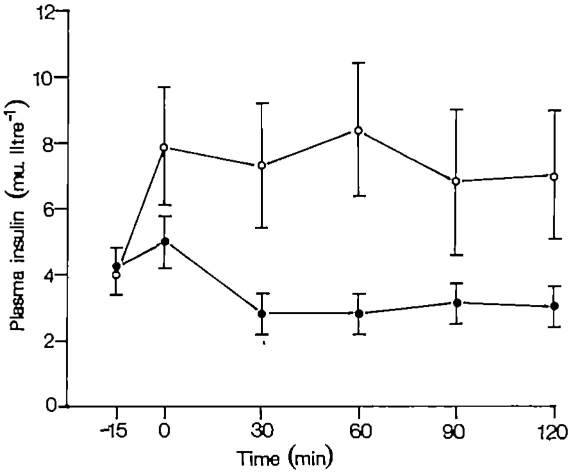

FIG. 1. Mean (± SEM) plasma insulin concentrations in control group of patients (closed circles) and phentolamine group of patients (open circles).

Changes in plasma insulin are shown in figure 1. The infusion of phentolamine for 15 min before surgery was associated with a significant increase ($P < 0.01$) in insulin from 4.0 to 7.9 mu. litre^{-1}. This increase persisted during surgery, whereas the control group showed the characteristic decrease in circulating insulin ($P < 0.05$) after 30 and 60 min of surgery. There was a significant difference ($P < 0.05$) in insulin concentrations between the two groups of patients after 30 and 60 min of surgery.

There was no significant change in either heart rate or mean arterial pressure during surgery in the control group of patients (fig. 2). However, the infusion of phentolamine before surgery was associated with a significant increase ($P < 0.01$) in heart rate from 75 to 98 beat min^{-1} and a significant decrease ($P < 0.01$) in mean arterial pressure from 82 to 73 mm Hg. These cardiovascular changes persisted throughout surgery in the α-blocked patients so that the mean arterial pressure was 59 mm Hg and the heart rate 93 beat min^{-1} after 120 min of surgery.

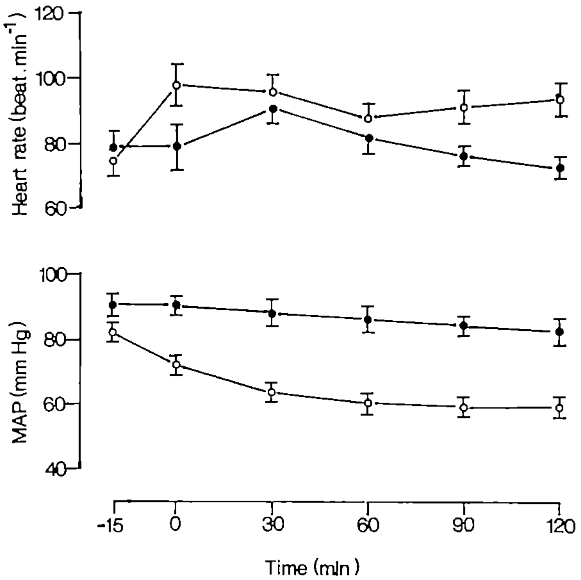

FIG. 2. Mean (± SEM) heart rate and mean arterial pressure (MAP) in control group of patients (closed circles) and phentolamine group of patients (open circles).

DISCUSSION

The failure of insulin secretion to respond to the hyperglycaemia of surgery is well documented and is assumed to be a result of the α-adrenergic inhibitory effects of the circulating catecholamines on the β-cells of the pancreas (Traynor and Hall, 1981). There is, however, little direct evidence to support this view and Allison, Tomlin and Chamberlain (1969) failed to observe any improvement in insulin response to i.v. glucose during a phentolamine infusion in two patients undergoing surgery. The results of the present study confirm the importance of adrenergic activity in modulating insulin secretion in the basal state before surgery (Robertson and Porte, 1973) and demonstrate that phentolamine significantly increases plasma insulin during surgery (fig. 1). Alpha-blockade produced only a two-fold increase in insulin compared with the control group, which agrees with the suggestion of Porte and Robertson (1973) that adrenergic control is exerted over a small storage pool of insulin.

It is tempting to infer that the increase in insulin in the phentolamine patients was responsible for the reduction in the glycaemic response to surgery by augmenting the utilization of glucose peripherally and by decreasing hepatic glucose production. It is important to note, however, that in the period before surgery there was no change in blood glucose in spite of an increase in plasma insulin from 4.0 to 7.9 mu. litre^{-1}. An increase in hepatic glycogenolysis is an important component of the hyperglycaemic response to surgery (Stjernström, Jorfeldt and Wiklund, 1981) and is thought to be mediated by stimulation of alpha-adrenoceptor (Antonis et al., 1967; Syvalahti et al., 1977). It is probable that inhibition of catecholamine-induced, hepatic glycogenolysis in the phentolamine patients was a major factor in reducing the hyperglycaemic response to surgery.

Alpha-adrenoceptors are involved in the control of secretion of other glycoregulatory hormones. Growth hormone release from the pituitary is inhibited by phentolamine (Imura et al., 1971), but this is unlikely to have influenced the glucose response in the present study since we have observed previously that growth hormone secretion during surgery does not alter the glucose response (Cooper et al., 1979). The adrenergic control of glucagon secretion is complex, but in general is increased by β-adrenergic stimulation (Unger and Orci, 1976). The administration of phentolamine in other stressful states such as exercise showed no effect on the plasma glucagon response (Galbo, Christensen and Holst, 1977). In a separate study, we have shown only a small, insignificant increase in plasma glucagon from 5.6 to 11.0 pmol litre^{-1} during pelvic surgery (unpublished observations), which suggests that glucagon secretion is unlikely to be a major factor in the regulation of blood glucose.

Lipolysis in adipose tissue is particularly sensitive to β_1-adrenergic stimulation, but is also subjected to inhibition by α-adrenoceptors (Fain, 1973). On this basis, phentolamine infusion during surgery would be expected to exacerbate lipolysis as shown by changes in plasma glycerol. The failure of α-blockade to increase plasma glycerol significantly in the present study may be attributed to the concurrent stimulation of the secretion of insulin, a potent antilipolytic hormone.

In conclusion, alpha-adrenergic blockade during surgery reverses the usual insulin suppression and attenuates the hyperglycaemia. The associated hypotension was well tolerated by the young, healthy patients used in this study. We suggest that the use of drugs during anaesthesia with α-blocking properties may confer metabolic advantages, in particular by increasing secretion of the key anabolic hormone insulin.

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EFFET DE LA PHENTOLAMINE SUR LA REPONSE METABOLIQUE A LA CHIRURGIE GYNECOLOGIQUE

RESUME

Nous avons étudié l'effet d'une perfusion de phentolamine 0,5 mg min^{-1} sur la réponse métabolique à la chirurgie gynécologique. Si l'on compare les résultats à ceux d'un groupe de patientes témoins, l'administration de la phentolamine s'accompagne d'une augmentation significative de la concentration plasmatique d'insuline après 30 et 60 min de chirurgie. La réponse hyperglycémique à la chirurgie est diminuée par le blocage alpha-adrénergique, mais ceci ne devient significatif qu'après 120 min de chirurgie. L'hypotension induite par l'administration de phentolamine a été bien tolérée.

DIE WIRKUNG VON PHENTOLAMIN AUF DIE METABOLISCHEN AUSWIRKUNGEN VON GYNAKOLOGISCHEN OPERATIONEN

ZUSAMMENFASSUNG

Wir untersuchten die Wirkung von Phentolamin-Infusionen (0,5 mg min^{-1}) auf die metabolischen Auswirkungen von gynäkologischen Operationen. Im Vergleich zu einer Kontrollgruppe fanden wir bei Patienten, die Phentolamin erhalten hatten, einen signifikanten Anstieg der Plasmainsulinkonzentration von 30 und 60 min nach der Operation. Der durch die Operation bedingte Abfall des Blutzuckers wurde durch alpha-adrenerge Blockade vermindert. Dies war aber erst 120 min nach der Operation signifikant. Den durch Phentolamin hervorgerufenen Blutdruckabfall vertrugen die Patienten gut.

EFECTO DE LA FENTOLAMINA EN LA RESPUESTA METABOLICA A LA INTERVENCION GINECOLOGICA

SUMARIO

Se investigó el efecto de la infusión de 0,5 mg min^{-1} de fentolamina en la respuesta metabólica a la intervención ginecológica. La fentolamina vino asociada con un incremento significativo de la concentración de insulina en el plasma después de transcurridos de 30 a 60 min de la intervención quirúrjica, en comparación con un grupo de pacientes de control. La respuesta glicémica a la intervención qurúrjica disminuyó mediante un bloqueo α-adrenérgico, pero esto tuvo carácter significativo después de haber transcurrido 120 min después de la operación. La hipotensión producida por la administración de fentolamina se toleró bien.

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ONE-LUNG VENTILATION OF CHILDREN DURING SURGICAL EXCISION OF HYDATID CYSTS OF THE LUNG

A. BARAKA, M. SLIM, A. DAJANI AND S. LAKKIS

SUMMARY

One-lung ventilation was used in 13 children, undergoing surgical excision of pulmonary hydatid cysts. Five had right-sided pulmonary cysts and eight had left cysts. An ordinary cuffed tracheal tube was introduced to the main bronchus of the healthy side. One-lung ventilation using 1–2% halothane in oxygen produced Pa_{O_2} values of 12.6–33.3 kPa and Pa_{CO_2} values of 4–6 kPa. After operation there was a high frequency of right upper lobe collapse in cases of selective right bronchial intubation, but this cleared completely within 3–4 days. The technique proved to be a simple and effective method of isolating and ventilating the healthy lung.

Infection with *Echinococcus granulosus* (hydatid disease) is endemic in countries of the Mediterranean basin. However, review of the recent literature emphasizes the global nature of the problem and the threat of spread into countries currently free from the disease (Editorial, 1976). Man serves as the intermediate host harbouring the larval stage, the "hydatid cyst" The liver, followed by the lungs, are the commonest sites for hydatid cyst formation (Jidejian, 1979). In children, pulmonary hydatid disease predominates (Slim et al., 1971; Slim and Akel, 1981).

Hydatid cyst fluid may be spilled inadvertently during surgery and may result in aspiration pneumonia. Also, if the fluid contains scolices, spillage will lead to the development of secondary cysts. Isolation of the surgical field from the surrounding healthy tissues must be ensured. In adults, the use of double-lumen tubes has solved the problem of protecting the intact lungs. In children such tubes are not available or practical. The present report describes a simple and safe technique of one-lung anaesthesia in 13 children undergoing surgical excision of pulmonary hydatid cysts. This was achieved by selective intubation of the main bronchus of the non-involved lung.

PATIENTS AND METHODS

The technique of bronchial intubation was used in 13 consecutive children undergoing surgical excision of hydatid cysts of the lung over a period of 2 yr. Their ages ranged from 3 to 14 yr. Five children had hydatid cysts of the right lung, and eight had left lung hydatid cysts (table I).

TABLE I. *Distribution of the hydatid cysts*

Right lung		Left lung	
Site	Number	Site	Number
RUL	1	LUL	3
RML	1	Lingula	1
RLL	3	LLL	4
Total	5	Total	8

All children were premedicated with atropine 0.3–0.6 mg and pethidine 2 mg kg^{-1} i.m., 45 min before induction. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and suxamethonium 2 mg kg^{-1}. The vocal cords were exposed by direct laryngoscopy and orotracheal intubation was performed using an Ohio cuffed tracheal tube of a size matching the age of the child. The tube was then pushed blindly into the main bronchus of the healthy lung and the cuff was inflated. The position of the tube was checked clinically by auscultation of both sides of the chest and confirmed by chest radiography. Anaesthesia was maintained with 1–2% halothane in oxygen, supplemented by the non-depolarizing muscle relaxant alcuronium. Ventilation was controlled manually using a modified Ayre's T-piece circuit (gas flow 3–6 litre min^{-1}) (Baraka et al., 1969). At the end of surgery, the

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ONE-LUNG VENTILATION OF CHILDREN DURING SURGICAL EXCISION OF HYDATID CYSTS OF THE LUNG

A. BARAKA, M. SLIM, A. DAJANI AND S. LAKKIS

SUMMARY

One-lung ventilation was used in 13 children, undergoing surgical excision of pulmonary hydatid cysts. Five had right-sided pulmonary cysts and eight had left cysts. An ordinary cuffed tracheal tube was introduced to the main bronchus of the healthy side. One-lung ventilation using 1–2% halothane in oxygen produced Pa_{O_2} values of 12.6–33.3 kPa and Pa_{CO_2} values of 4–6 kPa. After operation there was a high frequency of right upper lobe collapse in cases of selective right bronchial intubation, but this cleared completely within 3–4 days. The technique proved to be a simple and effective method of isolating and ventilating the healthy lung.

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Hydatid cyst fluid may be spilled inadvertently during surgery and may result in aspiration pneumonia. Also, if the fluid contains scolices, spillage will lead to the development of secondary cysts. Isolation of the surgical field from the surrounding healthy tissues must be ensured. In adults, the use of double-lumen tubes has solved the problem of protecting the intact lungs. In children such tubes are not available or practical. The present report describes a simple and safe technique of one-lung anaesthesia in 13 children undergoing surgical excision of pulmonary hydatid cysts. This was achieved by selective intubation of the main bronchus of the non-involved lung.

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residual non-depolarizing neuromuscular block was antagonized with a mixture of atropine 0.02 mg kg^{-1} and neostigmine 0.05 mg kg^{-1}.

All children were placed in the lateral decubitus position. The site and function of the tube were checked by the surgeon at thoracotomy. Twenty minutes after starting one-lung ventilation, arterial blood-gas tensions were measured in 10 patients. The hydatid cysts were identified and exposed and pads, soaked with aqueous Cetrimide (scolicidal agent), were packed around them. An incision was carefully made through the pericyst, the tube was withdrawn above the carina and gentle inflation of the lung helped to "deliver" the intact cyst. In case inadvertent rupture of the cyst occured during dissection, selective bronchial intubation was maintained until the cyst was completely excised. At the end of the procedure, adequate tracheobronchial

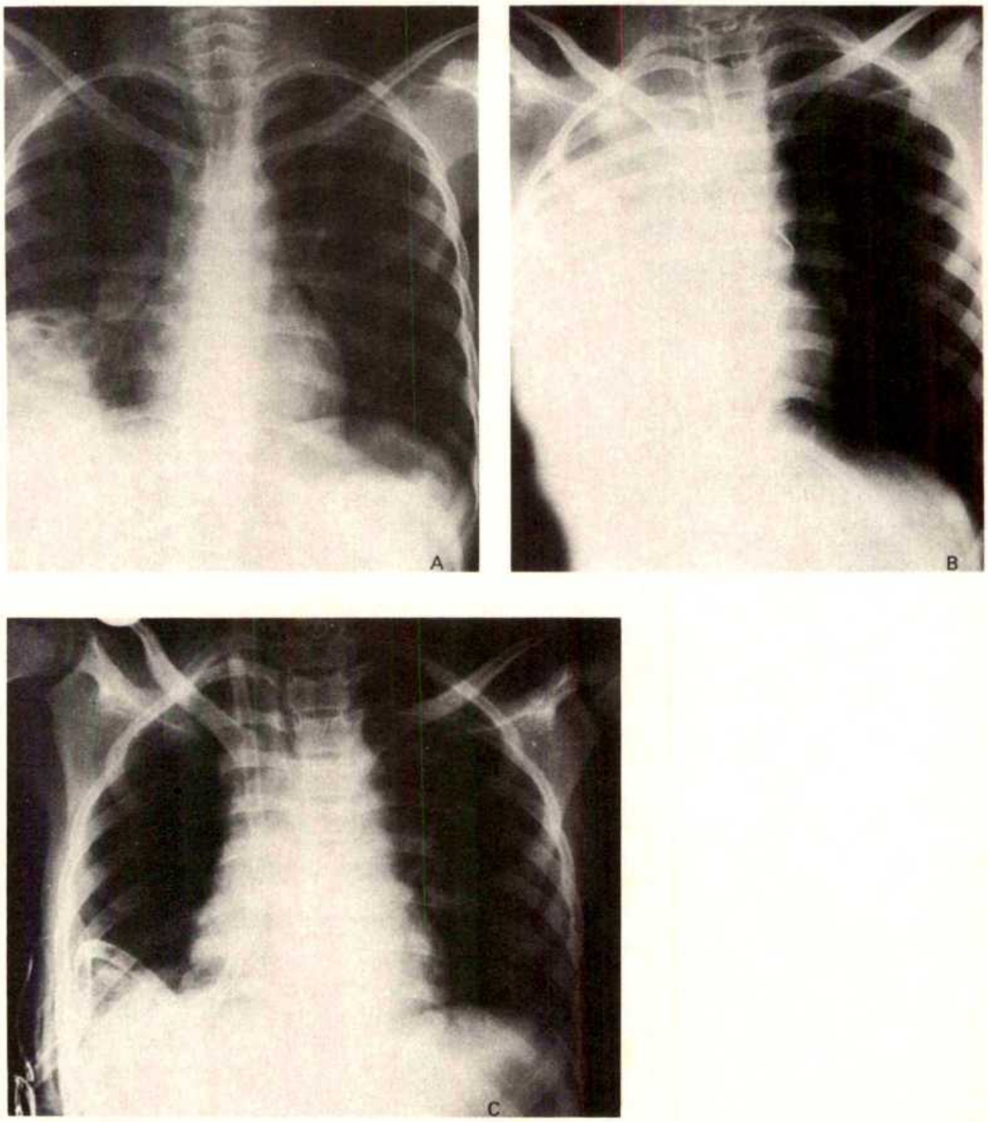

FIG. 1. A: Preoperative chest x-ray in a 12 yr-old child, revealing an infected hydatid cyst of the right lower lobe. B: Chest x-ray taken after the tracheal tube was introduced into the left main bronchus. The diseased right lung is collapsed and ventilation is limited to the left lung. C: Postoperative chest x-ray after surgical excision of the hydatid cyst and under-water seal drainage.

suction was carried out, both lungs were inflated and the chest was closed and drained under water seal. After operation the chest was x-rayed to detect any complications.

RESULTS

In all patients, selective bronchial intubation of the normal lung could be achieved successfully (fig. 1). The right bronchus was readily intubated in all children, while intubation of the left bronchus required two or three attempts and was facilitated by the use of a malleable metallic stylet to curve the distal end of the tube to the left.

The technique provided a motionless collapsed lung at thoracotomy which improved surgical exposure of the cyst. Eleven of the 13 cysts could be delivered intact, while only two cysts ruptured during dissection. Selective bronchial intubation succeeded in isolating the diseased from the healthy lung, thus preventing any possible transbronchial spread of hydatid fluid to the dependent normal lung. During one-lung anaesthesia Pa_{O_2} values were 12.6–33.3 kPa and P_{CO_2} 4–6 kPa (table II).

After operation four children of the eight who received right bronchial intubation developed right upper lobe collapse (fig. 2). In contrast, there was no collapse of the left lung following left bronchial intubation.

Complications after operation also occurred on the operated side. There were two cases of collapse and one pneumothorax on the right side. On the left side, there were three cases of collapse and one complete collapse of the left lung (fig. 3). The postoperative collapse was treated with intensive physiotherapy, humidified oxygen and broad-spectrum antibiotics and, in all cases, it cleared within 3–4 days. Follow-up chest x-ray showed complete expansion of both lungs.

TABLE II. *Results of arterial blood P_{O_2} and P_{CO_2}, 20 min after selective bronchial intubation*

	P_{O_2} (kPa)	P_{CO_2} (kPa)
	26.7	4.6
	33.3	4.5
	30.0	4.5
	26.6	5.0
	29.3	4.7
	13.6	4.6
	24.0	4.5
	22.0	4.0
	30.6	4.7
	12.6	6.0
Mean	24.9	4.7
SD	7.0	0.57

DISCUSSION

In patients undergoing surgical excision of pulmonary hydatid cysts, the healthy lung must be isolated in order to protect it against transbronchial spread of hydatid fluid should inadvertent rupture of the cyst occur during its dissection and exposure. In adults, the use of double-lumen tubes during pulmonary hydatid surgery has solved the problem of isolating the two lungs. In children, one-lung anaesthesia has been achieved previously by blocking the bronchus of the diseased lung by bronchoscopic insertion of a Fogarty arterial embolectomy catheter (Vale, 1969). Subsequent reports (Lines, 1969; Hogg and Lorhan, 1970; Cay et al., 1975; Rao et al., 1981) combined the use of the Fogarty catheter with endotracheal intubation or endobronchial intubation of the healthy side (table III).

The present report describes the use of an alternative method to achieve one-lung ventilation in 13 children undergoing hydatid lung surgery, by intubating the main bronchus of the non-involved lung. We have used successfully such selective contralateral bronchial intubation in children undergoing thoracotomy for other pulmonary lesions such as lung abscess, bronchiectasis or broncho–pleural fistula. The technique has been also used in the neo-

TABLE III. *Review of literature on one-lung ventilation in children undergoing thoracotomy*

Reference	No. of children	Technique
Vale (1969)	1	Fogarty catheter blocking and tracheal intubation.
Lines (1969)	1	Fogarty catheter blocking and bronchial intubation.
Hogg and Lorhan (1970)	1	Fogarty catheter blocking and tracheal intubation.
Cay and others (1975)	2	Fogarty catheter blocking and tracheal intubation.
Rao and others (1981)	1	Fogarty catheter blocking and tracheal intubation.
Rao and others (1981)	1	Fogarty catheter blocking and bronchial intubation.
Present series	13	Selective bronchial intubation.

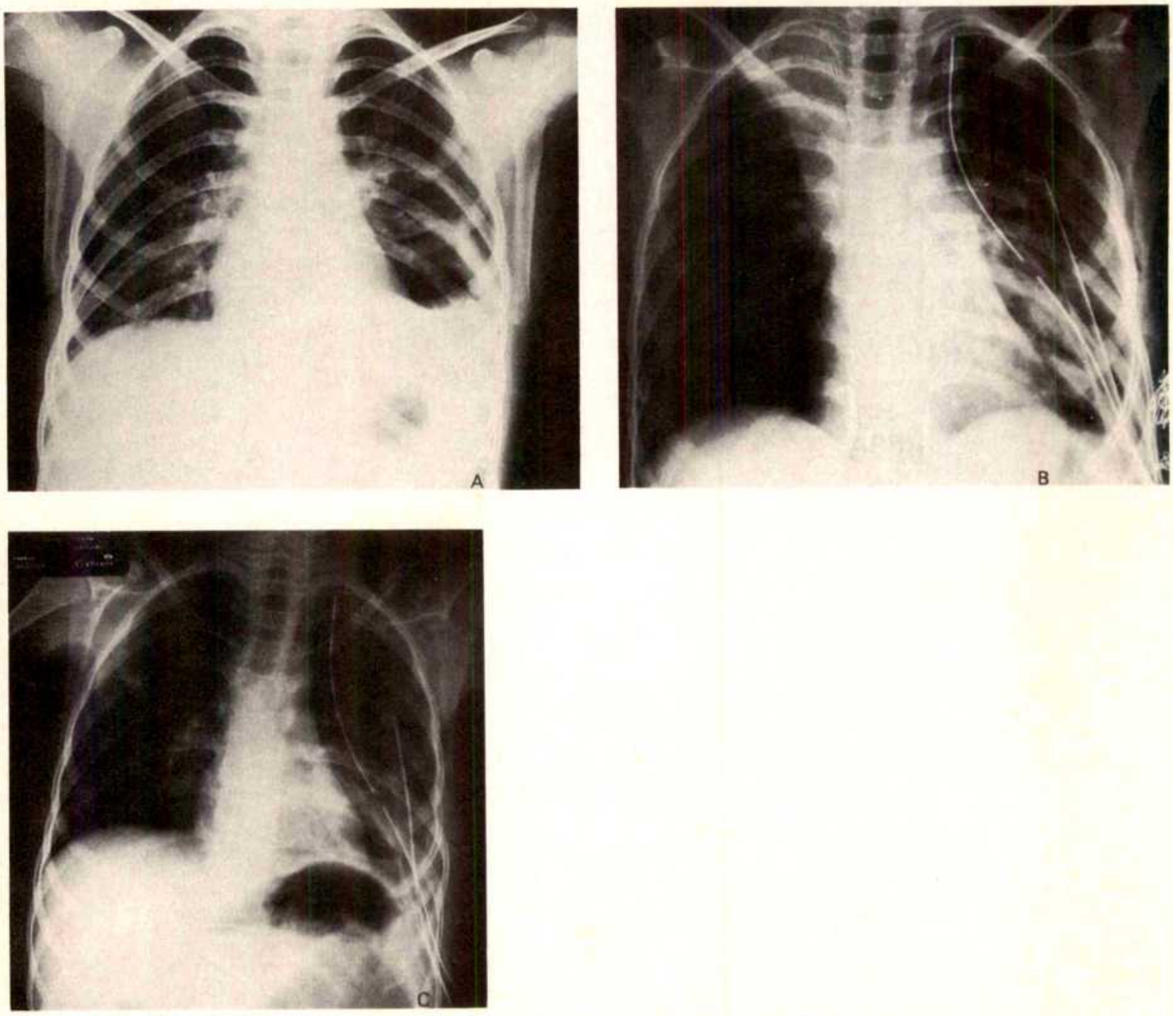

FIG. 2. A: Preoperative chest x-ray in a 10-yr-old child, revealing the typical findings of a ruptured infected hydatid cyst of the left lower lobe. The membrane of the endocyst is undulated at the air–fluid interface—"Water-lily sign". B: Postoperative chest x-ray showing complete collapse of the right upper lobe. C: Chest x-ray taken 3 days after operation, showing complete re-expansion of the collapsed right upper lobe.

nate for conservative non-surgical treatment of unilateral interstitial emphysema, as an alternative to lobectomy (Brooks et al., 1977).

Selective right bronchial intubation in children can be performed more readily than left bronchial intubation. A tracheal tube is more likely to enter the wider and more vertical right bronchus than the narrower and more obliquely placed left bronchus. After operation, however, right bronchial intubation was followed by a high frequency of right upper lobe collapse. The right upper lobe bronchus arises near the carina as an offshoot from the right main stem bronchus, while the left upper lobe bronchus arises further away from the carina as a bifurcation of the main trunk. That is why a tube pushed selectively down one bronchus is more likely to obstruct the orifice of the right upper lobe bronchus than that of the left.

Oxygenation and carbon dioxide elimination during one-lung ventilation have been studied extensively in experimental animals and in adults. A change from two- to one-lung ventilation does not result in a significant increase in Pa_{CO_2}, provided the total minute volume ventilation is maintained the same (Kerr, 1972). Although the minute volume is the principal factor determining carbon dioxide

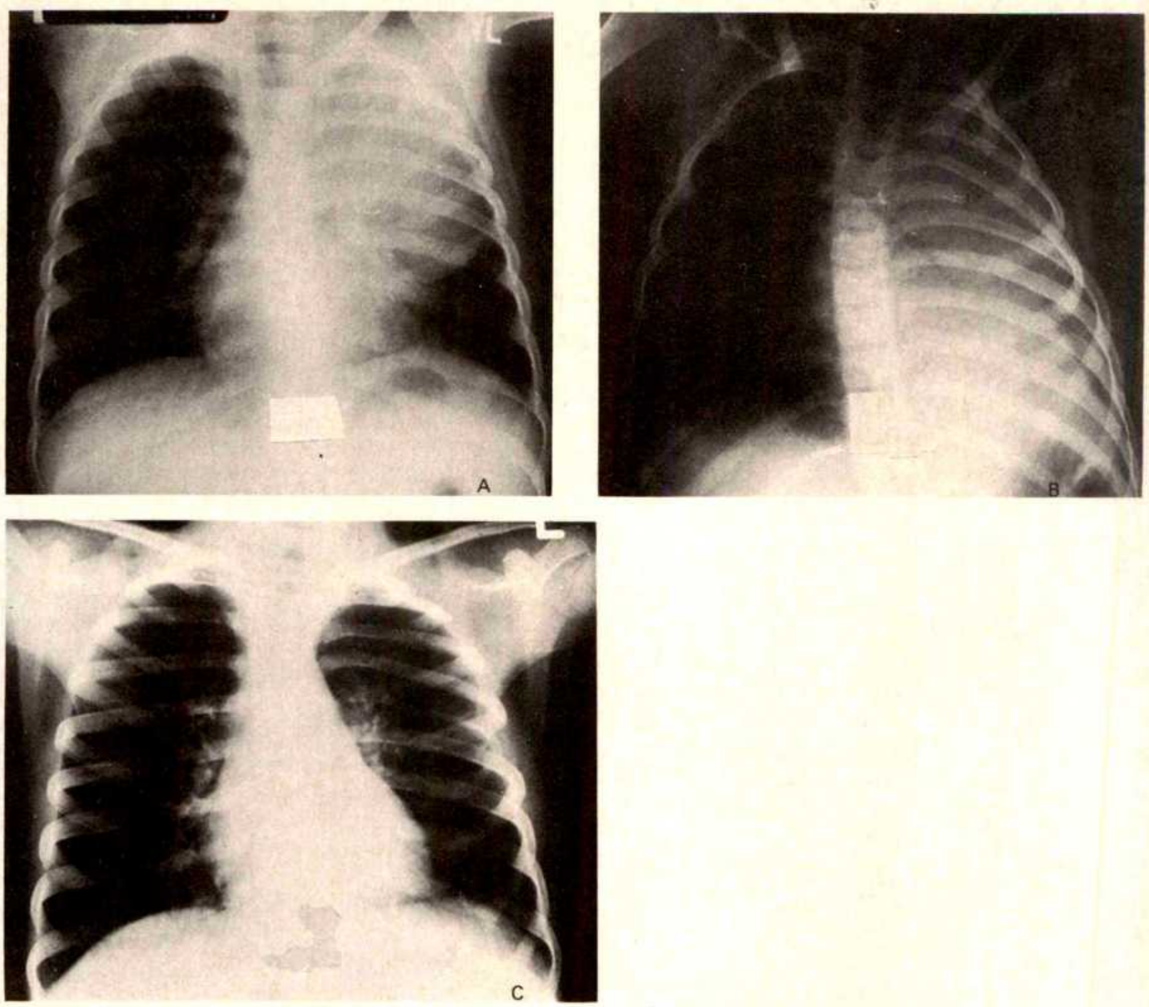

FIG. 3. A: Preoperative chest x-ray in a 9-yr-old child, revealing a large hydatid cyst in the left lung. B: Postoperative chest x-ray with evidence of complete collapse of the left lung. C: Postoperative chest x-ray showing complete re-expansion of the left lung.

elimination, arterial oxygenation during one-lung ventilation is affected by other factors, of which the inspired oxygen concentration and the distribution of pulmonary blood flow between the two lungs are the most significant. Continued perfusion of the non-ventilated lung will result in a gross shunt effect associated with hypoxaemia (Kerr, 1972; Kerr et al., 1974). This hypoxaemia may be mitigated in the lateral position by the gravitational redistribution of pulmonary blood flow resulting in preferential perfusion of the dependent ventilated lung (Nunn, 1977). Also, the hypoxaemia may be decreased by active hypoxic pulmonary vasoconstriction which results in a gradual redistribution of pulmonary blood flow away from the hypoxic collapsed lung into the ventilated lung. However, this redistribution response takes time to reach its maximum, and is therefore of little value as a means of minimizing arterial hypoxaemia secondary to one-lung ventilation during thoracotomy (Khanam and Branthwaite, 1973). In the children studied, Pa_{CO_2} could be maintained within the normal range during one-lung ventilation. Also, Pa_{O_2} was always greater than 12 kPa. It may be postulated that the hypoxic pulmonary vasoconstriction response is more active in the paediatric age group than in adults, resulting in a more rapid redistribution of the pulmonary blood flow from the collapsed diseased lung into the ventilated normal lung. However, a high inspired oxygen concentration must be maintained during one-lung ventilation, in order to ensure adequate Pa_{O_2}.

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VENTILATION SUR UN SEUL POUMON D'ENFANTS AU COURS DE L'EXCERESE CHIRURGICALE DE KYSTES HYDATIQUES DU POUMON

RESUME

La ventilation sur un seul poumon a été utilisée chez 13 enfants subissant l'excerèse chirurgicale de kystes hydatiques du poumon. Chez cinq d'entre eux, les kystes étaient à droite, et chez huit d'entre eux, à gauche. Une sonde d'intubation ordinaire à balonnet était introduite dans la bronche souche du côté sain. La ventilation sur un seul poumon, en utilisant de l'halothane à 1 ou 2% dans l'oxygène permettait d'atteindre des valeurs de Pa_{O_2} de 12,6–33,3 kPa et de Pa_{CO_2} de 4–6 kPa. Après l'intervention, la fréquence des atélectasies du lobe supérieur droit a été très grande en cas d'intubation sélective de la bronche souche droite, mais elles se levaient complètement en 3–4 jours. Cette technique s'est révélée simple et efficace pour isoler et ventiler le poumon sain.

EINSEITIGE BEATMUNG BEI DER OPERATIVEN ENTFERNUNG VON ECHINOKOKKUSZYSTEN DER LUNGE BEI KINDERN

ZUSAMMENFASSUNG

13 Kinder, die sich einer operativen Entfernung von Echinokokkuszysten unterziehen mußten, wurden einseitig beatmet. In 5 Fällen lagen die Zysten auf der rechten Seite und in 8 Fällen auf der linken. Wir führten einen Endotrachealtubus mit normaler Blocker manschette in den Hauptbronchus der gesunden Seite ein. Die einseitige Beatmung mit 1–2% Halothan in Sauerstoff erbrachte Pa_{O_2}– Werte von 12,6–33,3 k*Pa* und Pa_{CO_2}- Werte von 4–6 kPa. Postoperativ kollabierte sehr häufig der rechte obere Lungenlappen bei den Fällen mit rechtsseitiger Intubation, was sich aber innerhalb von 3–4 Tagen wieder vollständig zurückbildete. Die Technik erwies sich als einfache und wirksame Methode, um die gesunde Lunge sowohl abzuschalten als auch zu beatmen.

VENTILACION DE UN PULMON EN NIÑOS DURANTE LA EXCISION QUIRURJICA DE QUISTE HIDATIDICO DEL PULMON

SUMARIO

Se utilizó ventilación de un pulmón en 13 niños sometidos a intervención quirúrjica para la excisión de quiste hidatídico del pulmón. Cinco de ellos presentaron quistes del pulmón derecho y ocho quistes del pulmón izquierdo. En los bronquios del lado sano se introdujo un tubo traqueal ordinario y sujeto. La ventilación de un sólo pulmón, usando de 1% a 2% de halotano en oxígeno, produjo valores de 12,6–33,3 kPa para el Pa_{O_2} y de 4–6 kPa para el Pa_{CO_2}. Tuvo lugar una gran frecuencia de colapsos del lóbulo superior derecho, después de la operación, en aquellos casos de intubación selectivo del bronquio derecho, desapareciendo esto completamente en el transcurso de 3 a 4 días. La técnica en cuestión demostró ser un método sencillo y efectivo para aislar y ventilar el pulmón sano.

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HAZARDS OF NEOSTIGMINE IN PATIENTS WITH NEUROMUSCULAR DISORDERS

Report of two cases

W. BUZELLO, N. KRIEG AND A. SCHLICKEWEI

SUMMARY

In a 57-yr-old female with dystrophia myotonica, attempts to reverse residual non-depolarizing block with neostigmine 1.0 mg were only partially effective and the administration of a further dose (0.5 mg) produced long-lasting muscle weakness. The train-of-four response of this patient resembled that of a depolarizing block and suggested an alteration in the electrical properties of the muscle membrane. A 50-yr-old male with a 30-yr history of progressive muscle dystrophy, exhibited a tonic response to neostigmine in the evoked mechanomyogram during recovery from partial neuromuscular block. It is concluded that the type of reaction to neostigmine in patients with neuromuscular disease is unpredictable.

On account of their tonic response to depolarizing neuromuscular blocking drugs, various types of myotonia represent a source of potential hazard during general anaesthesia (Örndahl, 1962a; Paterson, 1962; Thiel, 1967; Mitchell, Ali and Savarese, 1978; Ellis, 1980). By facilitating depolarization of the motor end-plate, anticholinesterase drugs may cause contracture (Ellis, 1980). Since we are not aware of clinical reports on the effects of these drugs in myotonic patients, a report on adverse reactions to neostigmine in two patients with different neuromuscular disorders may be of interest.

CASE REPORTS

Dystrophia myotonica

The patient

A 57-yr-old female (65 kg) was admitted to another hospital for cholecystectomy. She was known to suffer from dystrophia myotonica with a prevailing dystrophic component. The first symptoms dated back to childhood, with predominant involvement of the muscles of her face and neck. During adolescence, she complained of contractures of her hands during milking. The diagnosis had been established 15 yr before the present admission, by both clinical signs and electromyography. During the past 5 yr, the patient was unable to lift her head and exhibited a typical myopathic face. Her sternocleidomastoid muscles were atrophic, and the muscles of her hands and forearms were much weaker than those of her upper arms. She had diplopia, cataracts, respiratory insufficiency and coronary heart disease. However, cardiomyopathy, a manifestation typical of dystrophia myotonica, was not present.

The anaesthetic procedure is illustrated in figure 1. The course of anaesthesia was uneventful during the 35-min operation and, in particular, no adverse effects of suxamethonium were reported. However, neuromuscular transmission was not monitored. The patient regained consciousness promptly, but severe respiratory insufficiency persisted during the following 1 h. The patient received neostigmine 1.0 mg with atropine 0.5 mg i.v. Her neuromuscular performance improved and the endotracheal tube was removed. Since head lifting was still impossible another neostigmine 0.5 mg was administered. A few minutes later inadequate breathing and cyanosis necessitated reintubation of the trachea and the patient was transferred to our intensive care unit. Several attempts to resume spontaneous ventilation failed and long-term mechanical ventilation was instituted.

On the 2nd and 3rd days after her operation it became increasingly difficult to synchronize the patient with the ventilator. As a result of this and because of her unstable arterial pressure, it was decided to use temporary myoneural blockade with pancuronium rather than larger doses of sedatives

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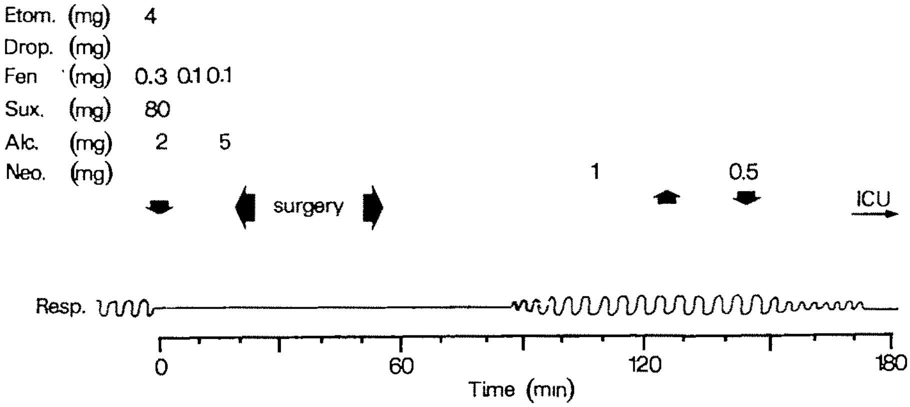

FIG. 1. Dystrophia myotonica (female patient, 56 yr, 65 kg). Premedication: atropine 0.5 mg, fentanyl 0.05 mg, droperidol 2.5 mg 30 min before induction of anaesthesia. Mechanical ventilation with 50% nitrous oxide in oxygen. ⬇= intubation, ⬆= extubation. Ventilation (Resp.) spontaneous (wavy line) or mechanical (——).

and narcotics to facilitate the mechanical ventilation. Furthermore, myoneural blockade during prolonged mechanical ventilation provided the opportunity to re-examine the patient's adverse response to neostigmine under controlled conditions including the monitoring of evoked twitch tension.

For this purpose the patient's forearm was secured by an appropriate splint, and a force displacement transducer was adjusted to her thumb with a preload providing maximum twitch response. Supramaximal train-of-four stimuli (2 Hz, 0.2 ms) were delivered to the ulnar nerve at the wrist 30–60 s apart. After a total of pancuronium 3.0 mg, given in incremental doses of 0.5 mg, twitch tension decreased to 16% of control (fig. 2). The train-of-four pattern showed the typical fade of a nondepolarizing block. At 45% recovery (57th min), neostigmine 1.0 mg was given with atropine 0.8 mg. No significant effect was observed, except on train-of-four fade. After another dose of neostigmine 0.5 mg with atropine 0.3 mg, complete neuromuscular block developed without concomitant increase of train-of-four fade. The block gradually assumed the characteristics of a depolarizing block. No muscarinic side-effects were observed after the injection of neostigmine and atropine. Spontaneous recovery of neuromuscular transmission commenced about 1 h later (160th min; not shown in figure 2). After almost 7 h, recovery was still incomplete (80% at 412th min).

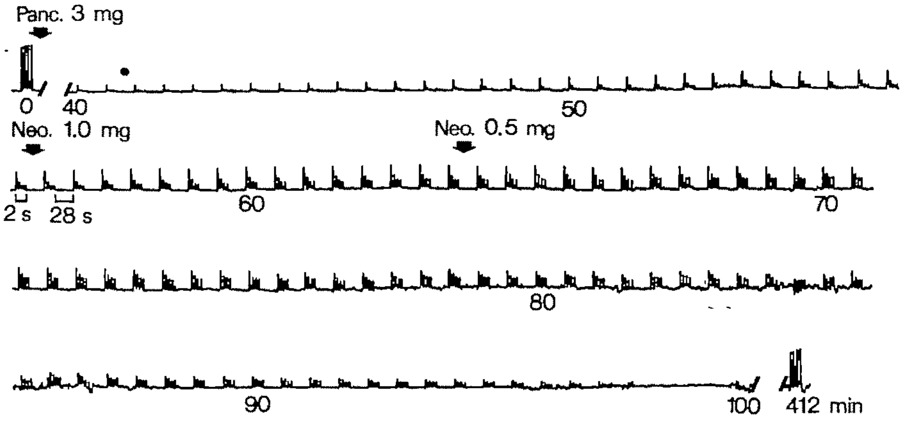

FIG. 2. Same patient as in figure 1. Twitch tension of right adductor pollicis muscle under repetitive train-of-four stimulation every 30 s. Normal response to a total of pancuronium (Panc.) 3 mg given in six divided doses of 0.5 mg, partial recovery of neuromuscular transmission after neostigmine (Neo.) 1.0 mg and recurrent long-lasting muscle weakness after a further administration of neostigmine 0.5 mg.

Pulmonary gas exchange improved subsequently, and the endotracheal tube was removed on the 5th day after operation. However, 12 h later recurrent respiratory failure and bronchial hypersecretion required reintubation of the trachea, and mechanical ventilation was resumed. The patient died on the 29th day following operation, as a result of intractable bronchopneumonia and severe hypoxaemia, hypercapnia and recurrent bradyarrhythmia.

Discussion

This patient was subject to four events: (i) apparently normal neuromuscular blockade after suxamethonium, (ii) normal sensitivity to pancuronium (and certainly to alcuronium), (iii) muscle weakness secondary to neostigmine which had been given to reverse residual alcuronium and pancuronium blockade, and (iv) inadequate use of the head-lift test in the recovery room, because head lifting had been impossible for 5 yr.

Dystrophia myotonica is a tonic muscle disease, and accordingly the patient had a history of tonic attacks. Hence one would have expected muscle contractures in association with suxamethonium. However, these were not reported by the attending anaesthetist. This may be because muscle atrophy is the progressive component of the disease rather than muscle contracture (Ellis, 1981). Muscle atrophy was also the predominant symptom in this patient and may have prevented the muscle contractures. This interpretation is supported by the fact that neostigmine was found to aggravate muscle paralysis rather than to reverse the block or to give rise to contractures. However, it cannot be excluded that some moderate tonic response to suxamethonium might have been detected if evoked twitch tension had been monitored (see patient with progressive muscle dystrophy, figure 3).

Impaired neuromuscular transmission secondary to the administration of neostigmine was observed both at the end of anaesthesia and during intensive care. However, this phenomenon is not only observed in muscle disease. In the absence of both neuromuscular disorder and neuromuscular blocking agents, Churchill-Davidson and Christie (1959) reported that during tetanic (25–50 Hz) stimulation the tension output was not maintained after the administration of neostigmine 1.25–2.5 mg. Larger doses (2.5–5 mg) caused a partial neuromuscular blockade, with decreases in the e.m.g. potentials, even at slow (2.5 Hz) rates of stimulation. Recently Hughes and Payne (1977) and Payne, Hughes and Al Azawi (1980) studied the effect of neostigmine on peak tetanic tension and tetanic fade (50 Hz) both without and after previous administration of non-depolarizing neuromuscular blocking drugs. The occurrence of muscle weakness depended on the fractional administration of neostigmine rather than on its total dose. The type of block created by neostigmine was always curariform in terms of decreased peak tetanic tension and marked tetanic fade. Concomitant decreases in single twitch tension were not a constant observation. Although the authors did not use train-of-four stimulation, the findings with stimulation at 2.5 Hz (Churchill-Davidson and Christie, 1959) make it reasonable to assume that train-of-four fade would have occurred when tetanic fade was present. The mechanism of neostigmine-induced muscle weakness is not yet completely understood.

In our patient with dystrophia myotonica, muscle weakness also developed after the second dose of neostigmine in the presence of residual non-depolarizing blockade. However, in terms of train-of-four response the characteristics were those of a partial depolarizing block (fig. 2). Furthermore, the

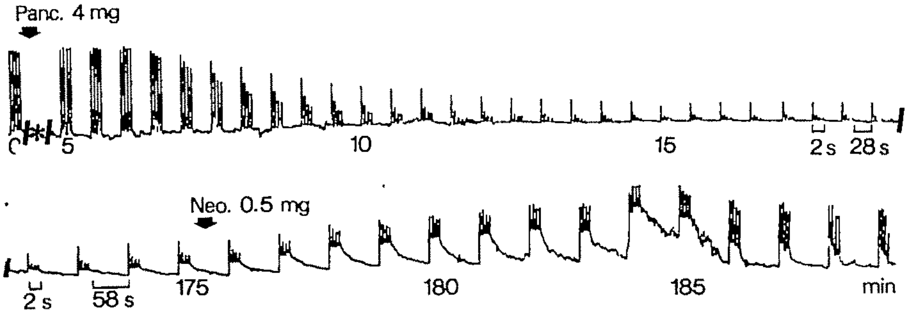

FIG. 3. Progressive muscle dystrophy (male patient, 50 yr, 59 kg). Twitch tension of left adductor pollicis muscle under repetitive train-of-four stimuli 30 s (upper tracing) and 60 s (lower tracing) apart. Normal response to pancuronium (Panc.), tonic response to neostigmine (Neo.).

amount of block was greater and the duration was much longer than in previous studies (Churchill-Davidson and Christie, 1959; Hughes and Payne, 1977; Payne, Hughes and Al Azawi, 1980).

Apparently, while interfering with partial non-depolarizing neuromuscular blockade, neostigmine may impair neuromuscular transmission by different mechanisms, depending on the presence or absence of neuromuscular disease. We do not believe that in the latter case the increase in blockade with concomitant reversal of train-of-four fade (fig. 2) was simply attributable to cholinesterase inhibition and excess acetylcholine at the motor end-plate. This view is supported by two unpublished observations we have made in more than 50 patients without neuromuscular disease: (i) neostigmine 0.015 mg kg^{-1} given to reverse partial non-depolarizing blockade always counteracted both depression of twitch and train-of-four fade. Reversal of train-of-four fade with a concomitant decrease in twitch tension was never observed. (ii) If suxamethonium was given in a dose sufficient to increase partial non-depolarizing block (0.5 mg kg), the decrease of tension output was always associated with increasing train-of-four fade, that is under these conditions suxamethonium never produced a "depolarizing block". The tracings from this patient with dystropia myotonica fit neither into these findings nor into those of Hughes and Payne (1977), and Payne, Hughes and Al Azawi (1980). Therefore, it is most likely that the particular pathology of the muscle fibre in terms of altered electrical properties of the muscle membrane or dysfunction of the sarcoplasmic reticulum are responsible for this type of adverse reaction since electrolyte imbalance and hypothermia can be excluded.

Progressive muscle dystrophy

The patient

A 50-yr-old man (59 kg) had a history of progressive muscle dystrophy. The diagnosis had been established 30 yr earlier and confirmed by biopsy. The disease involved the muscles of the shoulders, arms, lower spine, pelvis and legs. He had difficulty in maintaining an upright posture and his gait was short-stepped. The patient was admitted to hospital for surgical treatment of a non-malignant prepyloric stenosis. After premedication with atropine 0.5 mg, pethidine 50 mg and flupromazine 10 mg, anaesthesia was induced with thiopentone 300 mg, fentanyl 0.5 mg and droperidol 12.5 mg. Pancuronium 4 mg was given to produce neuromuscular blockade before endotracheal intubation. Anaesthesia was maintained with 67% nitrous oxide in oxygen and ventilation was controlled mechanically. Fentanyl 0.85 mg in fractional doses and pancuronium 1.0 mg were administered during surgery. Neuromuscular transmission was not monitored. The courses of surgery and anaesthesia were uneventful. At the end of anaesthesia the residual neuromuscular block was not reversed because the patient had been scheduled for prophylactic postoperative mechanical ventilation until the following day.

Alerted by the case of dystrophia myotonica and in consideration of the possibility that the patient might require further anaesthesia and surgery in the future, we took advantage of the mechanical ventilation which was in progress to investigate his response to pancuronium and neostigmine. Two-and-a-half hours after the end of anaesthesia and under sedation with droperidol and fentanyl a total of pancuronium 4 mg (approximately 0.07 mg kg^{-1}) was administered in divided doses of 0.5, 0.5 and 3.0 mg while the evoked twitch tension was monitored (fig. 3). The maximum effect (24% residual transmission) was obtained within 15 min. Increments of pancuronium 1.0 and 0.5 mg were given after 1 and 2 h at 46 and 38% recovery respectively (not depicted in figure 3). From the 172nd min spontaneous recovery of neuromuscular transmission was associated with a moderate, but increasing, elevation of the base-line during each train-of-four response. A test-dose of neostigmine (0.5 mg) given at 40% recovery (176th min) produced almost immediate cessation of the train-of-four fade and a prompt increase of twitch tension to 84% of control within 9 min. The reversal of neuromuscular block was associated with an increase in the base-line to 70% of the peak tension output (184th min). The base-line returned to normal between the 10th and 15th min after neostigmine and, concomitantly, twitch tension decreased to 77% of control (187th min). Four hours after the first dose of pancuronium, neuromuscular transmission was restored completely (train-of-four ratio = 1.0). On the 1st day after operation spontaneous ventilation was restored and the endotracheal tube removed. The further clinical course was uneventful.

Discussion

Since pancuronium 4 mg did not provide total neuromuscular blockade it would appear that the sensitivity of this patient to pancuronium was normal and although the duration of neuromuscular blockade was prolonged we have observed similar recovery periods in healthy individuals. The administration of neostigmine to reverse the residual non-depolarizing blockade gave rise to a tonic response in the indirectly stimulated muscle. This finding was surprising because progressive muscle dystrophy is not typically a tonic disease and the patient gave no history of tonic attacks.

Basically, in the evoked mechanomyogram the tonic response of skeletal muscle to indirect electrical stimulation is reflected by an increase in the base-line, because the electrical activity of the muscle fibres diminishes more rapidly than the mechanical contraction (Örndahl, 1962b). In severe cases this type of reaction may occur after any kind of stimulation and may cause acute peripheral respiratory failure. It has been suggested that this phenomenon might be a result of the presence of several end-plates on a single muscle fibre (Örndahl, 1962b). However, this view is challenged by the observation that non-depolarizing myoneural blockers or spinal anaesthesia may not prevent, or reverse, contractures caused by direct surgical stimulation (Ellis, 1980). More recent investigation indicates that the underlying pathology of myotonia is related to the sarcotubular system, rather than to the neuromuscular junction (Buxton, 1980). In particular, the tonic response of our patient is explained on the basis of an increased agonistic potential acting on muscle fibres with electromechanical imbalance. So far this mechanomyographic finding does not appear to be of major clinical relevance, since there were no visible muscle contractures. However, neostigmine 0.5 mg was a small dose, and the response to the higher doses usually given for reversal of non-depolarizing block or in the treatment of ileus remains open to question.

GENERAL COMMENT

In addition to the problems peculiar to these two entirely different types of muscle disease, which have been discussed above, there are several aspects of this topic which relate to clinical anaesthesia in general.

(i) Although these are rare diseases, the management of patients with muscle disease is not restricted to specialized centres. Any anaesthetist may encounter such patients and will have to manage them without having particular experience in this field.

(ii) It is impossible to predict the individual sensitivity to non-depolarizing neuromuscular blocking drugs, the type of response and the individual sensitivity to depolarizing neuromuscular blocking drugs, and the type and degree of the response to neostigmine. Therefore it is of clinical interest to obtain reliable information on a particular patient's response to these drugs under controlled conditions to delineate any future requirement for myoneural blocker and neostigmine. The results of a neostigmine test may be important if the use of this drug is considered for the treatment of ileus.

(iii) In anaesthesia for patients with neuromuscular disease, attempts should be made to avoid the use of myoneural blocking drugs in favour of regional analgesia alone or in combination with general anaesthesia.

(iv) If the use of neuromuscular blocking drugs is mandatory their administration should be subject to meticulous monitoring with the aid of a peripheral nerve stimulator to avert the need for reversal agents. The new short-acting drugs like Org NC 45 (Bowman and Norman, 1980) and atracurium (Payne and Hughes, 1981) may be more advantageous than the relatively long-acting agents in current use.

(v) Despite various reports on successful reversal of residual non-depolarizing neuromuscular blockade by anticholinesterase agents in myotonic patients (Coleham and Davies, 1964; Dalal et al., 1972), this technique is ill-advised because of the neuromuscular and systemic complications of the disease. Because of the cardiac pathology frequently present in patients with muscle disease, anticholinesterase agents may precipitate severe bradyarrhythmias (Church, 1967; Kilburn, Eagen and Heyman, 1959). Residual curarization should only be treated by mechanical ventilation.

(vi) It is most likely that the untoward reactions observed with neostigmine may occur with any anticholinesterase agent.

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LES RISQUES DE LA NEOSTIGMINE CHEZ LES PATIENTS ATTEINTS D'ANOMALIES NEUROMUSCULAIRES

A propos de deux cas

RESUME

Chez une femme de 57 ans atteinte de *dystrophie myotonique*, les tentatives d'antagonisation d'un bloc non dépolarisant résiduel par 1 mg de néostigmine n'ont été que partiellement efficaces et l'administration d'une dose supplémentaire (0,5 mg) a entraîné une faiblesse musculaire prolongée. La réponse au train de quatre chez cette patiente resemblait à celle d'un bloc dépolarisant et évoquait une altération des propriétés électriques de la membrane musculaire. Un homme de 50 ans avec une histoire longue de 30 ans de *dystrophie musculaire* progressive, a objectivé une réponse tonique à la néostimine sur le mécanomyogramme évoqué au cours de la récupération d'un bloc neuromusculaire partiel. Nous en concluons que le type de réaction à la néostigmine chez les patients atteints de maladies neuromusculaires est imprévisible.

GEFAHREN DER ANWENDUNG VON NEOSTIGMIN BEI PATIENTEN MIT NEUROMUSKULÄREN ERKRANKUNGEN

Bericht über zwei klinische Fälle

ZUSAMMENFASSUNG

Bei einer 57 Jahre alten Patientin mit nahezu lebenslanger Anamnese einer Dystrophia myotonica wurde nach Cholecystektomie die Aufhebung des Überhangs einer nicht depolarisierenden neuromuskulären Blockade mit Neostigmin versucht. Eine Dosis von 1,0 mg war nahezu wirkungslos, während auf eine zweite Dosis von 0,5 mg eine über mehrere Stunden anhaltende neuerliche neuromuskuläre Blockade erfolgte. Bei dieser Patientin bot die Vierfachreizantwort das Bild eines Depolarisationsblocks. Dies läßt daran denken, daß die elektrischen Eigenschaften der Muskelmembran verändert waren. Bei einem 50 Jahre alten Patienten mit einer 30 Jahre zurückreichenden Anamnese einer progressiven Muskeldystrophie führte Neostigmin während der Erholung von einem partiellen Pancuroniumblock zu einer tonischen Reaktion im evozierten Mechanomyogramm. Die Reaktion von Patienten mit neuromuskulären Erkrankungen auf Neostigmin ist dem-nach unvorhersehbar.

PELIGROS DE LA NEOSTIGMINA EN PACIENTES CON DESORDENES NEUROMUSCULARES

INFORME DE DOS CASOS

SUMARIO

Los intentos efectuados para invertir el bloqueo no despolarizante y remanente con 1,0 mg de neostigmina, en una paciente de 57 años de edad con *distrofia miotónica*, fueron certeros tan sólo parcialmente y la administración de una dosis complementaria de 0,5 mg produjo una prlongada debilidad muscular. La respuesta-de-cuatro impulsos de este paciente asemejó la de un bloqueo despolarizante y sugirió una alteración en las propiedades eléctricas del músculo. Un paciente masculino de 50 años de edad, con un historial de 30 años de *distrofia muscular progresiva*, mostró una respuesta tónica a la neostigmina en el mecanomiograma evocado, durante la recuperación del bloque neuromuscular parcial. La conclusión es que el tipo de reacción a la neostigmina por parte de pacientes con enfermedades neuromusculares es impredecible.

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EXTERNAL JUGULAR VEIN ACCESS TO THE CENTRAL VENOUS SYSTEM – A TRIAL OF TWO TYPES OF CATHETER

G. S. Riddell, I. P. Latto and W. S. Ng

SUMMARY

The central placement rate of central venous catheters inserted via the external jugular veins was assessed using two different types of catheter. In 50 patients a catheter-through-cannula design was used, in 50 a catheter-through-needle design; central placement rates were 72% and 60% respectively. Complications were few and never serious. The catheter-through-cannula design is recommended.

Several authors have reported a low frequency of central placement with catheters inserted through the external jugular vein. The high failure rate may be caused by anatomical difficulties and by the nature of the catheter used. The anatomical factors include the presence of an acute angle between the subclavian and the external jugular vein, the presence of valves, constriction of the vein as it penetrates fascial layers and angulation at junctions with tributaries.

We have investigated the central placement rate from the external jugular vein with two different types of catheter.

METHOD

Anaesthetized adult surgical patients requiring a central venous catheter were studied consecutively.

Each patient was placed 20° head-down with the head turned away from the proposed side of cannulation, and the arms placed by the side. The suitability of the external jugular vein for insertion was assessed. If the vein was neither palpable nor visible, cannulation was not attempted. Alternate left- and right-sided cannulations were performed.

Two types of catheter were used: a flexible catheter-through-cannula (CTC) (Wallace Piggy Back catheter No. 3316, Wallace, Colchester, Essex) with a rounded end and two side holes (Farman, 1976) and a catheter-through-needle (CTN) (Drum Cartridge No. 4719, Abbott Laboratories, North Chicago, Illinois) with a central rigid stilette.

Catheterization was performed under sterile conditions. The vein was distended by holding the lungs in inflation and placing a finger on its lower portion. The needle was inserted through the skin over the vein, well above the clavicle and advanced until the vein was entered.

If resistance was encountered when threading CTC centrally, the catheter was rotated, light pressure applied to the skin just above the clavicle and, if necessary, fluid was injected as the catheter was advanced. If CTN was difficult to thread, the stilette was removed and further manipulation attempted. CTN was inserted approximately two turns of the drum (8–10 cm). No attempt was made to force the catheters centrally or use forceps to advance them (McKenzie and Latto, 1981).

Once it had been confirmed that blood could be aspirated from the catheter, by partial withdrawal if necessary, it was fixed in position. If central placement was impossible, the catheter was left in position. In each case any difficulty in visualizing, palpating, or locating the vein with the needle or problems threading the catheter were recorded. A chest x-ray was taken to determine the position of the catheter tip.

Results were analysed using the Chi-squared test.

RESULTS

One hundred and fourteen patients were studied. In 14 of these it was not possible to cannulate the vein, because the vein was neither visible nor palpable (11) or the left vein was not visible and a carotid artery aneurysm was near the vein on the right (one), or a superficial haematoma was produced (two).

Twenty-five right and 25 left external jugular veins were catheterized with each type of catheter (table I). Successful central (intrathoracic) placement was achieved in 36 of 50 (72%) with CTC and

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TABLE I. *Details of catheter placements. †Differences not significant*

	Central placement rate		Position of non-central catheters			
Side	CTC	CTN	CTC		CTN	
Right	17† (68%)	17† (68%)	Superficial cervical	1	Superficial cervical	1
			Junction external jugular and subclavian	3	Junction external jugular and subclavian	3
			Turned back in external jugular	2	Turned back in external jugular	2
			Ipsilateral axillary	1	Ipsilateral axillary	1
			Contralateral internal jugular	1	External jugular	1
Left	19† (76%)	13† (52%)	Superficial cervical vein	3	Superficial cervical vein	3
			Junction external jugular and subclavian	1	Junction external jugular and subclavian	8
			Ipsilateral axillary vein	2	Contralateral internal jugular	1

30 of 50 (60%) with CTN (table II).

The frequency of difficult threading and eventual success is shown in table II. It was possible to aspirate blood after placement in all cases using CTC (with two side holes), but CTN had to be partially withdrawn in 12 patients (24%) before blood would flow and three of these 12 were seen on x-ray to be central after adjusting the position.

In one patient from each group, a superficial haematoma was produced, preventing successful insertion. A small haematoma occurred in one patient, but insertion was successful. The stilette was difficult to remove from two CTN, one where the catheter had gone down the ipsilateral axillary vein and one which had failed to negotiate the external jugular–subclavian vein junction. No other complications occurred.

DISCUSSION

The central placement rate in this study was 72% with CTC and 60% with CTN. The use of the left or right vein did not influence success significantly. Dietel and McIntyre (1971) reported a success rate of 50% and Malatinsky and others (1976) a success rate of 70% when using the external jugular vein. A 90% success rate was observed by Giesy (1972) using a soft, pliable silicone elastomer catheter injected by the fluidic technique. A 96% success was described with the J-wire apparatus (Blitt et al., 1974), while Abadir, Ung and Chandry (1979) report 97% success in inserting Swan–Ganz catheters via the external jugular vein again using a J-wire. Belani and others (1980) used the J-wire technique, but reported a central placement rate of only 76%. Schwartz and others (1981) compared the use of a flexible J-wire with a flexible straight wire and found greater success rate with the J-wire (86% compared with 61%). The J-wire catheter itself is fairly stiff, which may make vein perforation after long-term use more likely.

In our study, a flexible CTC was used because we hoped that it would allow easy placement in a central position without using the more expensive and less readily available J-wire apparatus. Flexibility, however, although intended to allow negotiation of angles, reduces the longitudinal force which can be applied to advance the catheter without causing a concertina effect either inside the protective sleeve or inside the vein. Longitudinal manipulation of CTN should be easier with the advantage of a moderately flexible tip, although this catheter was not designed for this route. A flexible stilette inside

TABLE II. *Difficult threading and total successful placements (No. of patients). † Difference not significant*

Catheter	Resistance to threading centrally	No. of these finally successful	Total successful placements
CTC (50)	25	16 (64%)	36† (72%)
CTN (50)	27	10 (37%)	30† (60%)

the CTC might improve the central placement rate by providing extra longitudinal stability. Free flow through CTN was more difficult to achieve without partially withdrawing the catheter, perhaps because the single end-hole had impinged on the vein wall.

CTN designs are not recommended for clinical use (D.H.S.S., 1972). While recognizing the problems associated with this method of inserting catheters, we used this catheter for the external jugular vein because we felt that the physical properties of the catheter (perhaps simulating a Seldinger wire) might be successful for this route and an alternative method of insertion could then be designed. Our results, however, have not confirmed this. When CTN was passed via the basilic vein as originally intended, a central placement rate of 70.3% was reported (Ng and Rosen, 1973) and—especially important—no serious complication was described. Our results for the Wallace CTC via the external jugular vein are as good, and we suggest that this catheter, via this route, is an effective and safe alternative to the still widely used CTN in the arm.

The use of the J-wire technique still provides the highest quoted placement rate for insertion of central venous catheters by the external jugular route (Blitt et al., 1974) but CTC provides an alternative. We suggest that the J-wire be used when CTC has failed. The use of 5-cm cannulae in the external jugular vein has been found under certain circumstances to give a reasonable indication of right atrial pressure (Briscoe, 1973; Stoelting, 1973). Accurate measurements of central venous pressure using CTC which have failed to negotiate the subclavian–external jugular vein junction, may be possible. This aspect is currently under more detailed investigation.

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ACCES AU RESEAU VEINEUX CENTRAL PAR LA VEINE JUGULAIRE EXTERNE: UN ESSAI DE DEUX SORTES DE CATHETERS

RESUME

Nous avons mesuré la fréquence de mise en position centrale de cathéters veineux insérés par la veine jugulaire externe, en utilisant deux différentes sortes de cathéters. Chez 50 patients, nous avons utilisé un cathéter coulissant dans une cannule et chez 50 autres cathéter coulissant dans une aiguille; les fréquences de mise en position centrale étaient respectivement de 72% et 60%. Les complications sont restées peu nombreuses et jamais graves.

ZUGANG ZUM ZENTRALVENENSYSTEM ÜBER DIE VENA JUGULARIS EXTERNA—ERPROBUNG VON ZWEI KATHETERARTEN

ZUSAMMENFASSUNG

Wir untersuchten die zentrale Plazierungsrate von zwei verschiedenen Arten von Zentralvenenkathetern, die über die Vena jugularis externa vorgeschoben wurden. Bei 50 Patienten wurde ein "Katheter-mittels-Knulen-System" und bei 50 Patienten ein "Katheter-durch-Nadel-System" verwendet. Die zentrale Plazierungsrate war 72% bei ersterem und 60% bei letzterem System. Es traten nur wenige Komplikationen auf, die in keinem Falle ernst waren.

ACCESO EXTERNO AL SISTEMA VENOSO CENTRAL A TRAVES DE LA VENA JUGULAR— UNA PRUEBA DE DOS TIPOS DE CÁTETERES

SUMARIO

Se evaluó el ritmo de colocación central de cáteteres venosos centrales introducidos a través de las venas jugulares externas, usando dos tipos de cáteteres diferentes. En 50 de los pacientes se utilizó un diseño de cáteter vía cánula y en otros 50 un diseño de cáteter vía aguja. Los ritmos de colocación central fueron de 72% y de 60% respectivamente. La complicaciones fueron pocos y nunca serias.

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EFFECTS OF VARYING INSPIRATORY FLOW WAVEFORM AND TIME IN INTERMITTENT POSITIVE PRESSURE VENTILATION: PULMONARY OEDEMA

A. B. BAKER, J. B. THOMPSON, J. TURNER AND P. HANSEN

SUMMARY

Greyhound dogs were given oleic acid i.v. to induce controlled pulmonary oedema. These animals were then studied using intermittent positive pressure ventilation (IPPV) with four different inspiratory flow waveforms, each at three different inspiratory times, in a fixed respiratory cycle of 4 s at a constant tidal volume. Although there were statistically significant differences in airway and oesophageal pressures between the different waveforms and times, there was little variation in the other physiological parameters studied except for arterial carbon dioxide tension (Pa_{CO_2}) which showed statistically significant improvement with reversed ramp and sine wave inputs and at the longer inspiratory time of 2.2 s. Venous admixture ($\dot{Q}_s/\dot{Q}_t$) was also less with the longer inspiratory time of 2.2 s.

Following the successful demonstration of improved physiological variables with certain inspiratory flow waveforms and times in IPPV in normal dogs (Baker et al., 1977; Baker, Colliss and Cowie, 1977; Baker, Cowie and Colliss, 1977) a study of these variables with similar alterations in inspiratory flow waveform and time has been carried out in dogs subjected to pulmonary oedema.

Human pneumonopathy (Harley, 1961) or the adult respiratory distress syndrome (ARDS) (Ashbaugh et al., 1967) is normally treated with IPPV and any means of improvement in this technique would be most useful in the management of patients with this disorder. Because of the wide variation in clinical pneumonopathy it has not been feasible to study the influence of different patterns of IPPV. Thus the animal model has been used by many investigators.

Injection of oleic acid i.v. was first used as a model for the fat embolism syndrome and its subsequent pulmonary oedema (Ashbaugh and Uzawa, 1968; Baker, Kuenzig and Peltier, 1969; Uzawa and Ashbaugh, 1969; King et al., 1971), although later this technique has been accepted as a valid model for pneumonopathy or ARDS (Derks and Jacobovitz-Derks, 1977; Scharf and Ingram, 1977; Osher et al., 1978; Cheney, Huang and Gronka, 1979; Griffith et al., 1979; Ehrhart and Hofman, 1981). One of the problems with these studies has been the rapid demise of the animals because of the severity of the pulmonary oedema induced. For the present study a period of stable survival for 10–12 h after the injection of oleic acid was necessary so that the various random combinations could be compared without time-dependent considerations.

METHODS

Because of availability the animal chosen for this study was the greyhound racing dog. Initially a small series of tests was made with different doses of oleic acid injected i.v. via a pulmonary artery catheter to establish a stable period of pulmonary oedema. The dose used for the study was established at 0.05 ml kg^{-1}, which was found to cause an initial steady deterioration in Pa_{O_2} over the first 2 h after injection and then a relatively stable state for approximately 10 h with only a very minor further deterioration in Pa_{O_2} (fig. 1). All animals in the initial study were x-rayed before the injection and at hourly intervals thereafter. From this it was shown that the radiological evidence of pulmonary oedema was little altered after 2 h, confirming the arterial oxygen tension figures. In the definitive study the animals' chests were x-rayed before the injection of oleic acid, at 2 h and at 8 h after injection for confirmation of the pulmonary oedema. In all animals lung histology was examined after sacrifice

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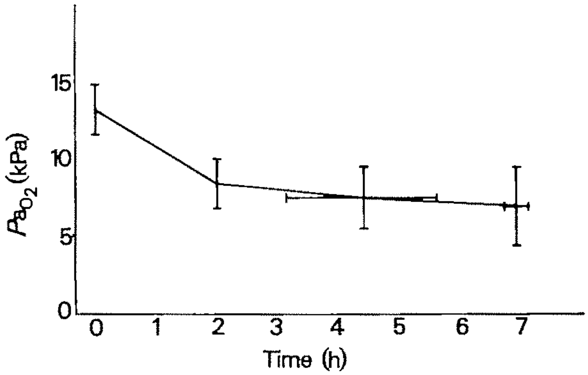

FIG. 1. Arterial oxygen tension (mean ± SD) for all experimental dogs ventilated with the T_I inspiratory flow waveform combination. Time 0 h = immediately before the injection of oleic acid; 2 h = immediately before the first random waveform combination. The third point, with a mean of approximately 4.5 h, is the point at which the T_I waveform combination occurred randomly and the final point, with a mean of almost 7 h, was the final control reading with the T_I waveform combination. This figure demonstrates that there was an initial period of deterioration as a result of the injection of oleic acid, but that after the first 2 h there was only minimal further deterioration.

at the termination of the experiment (fig. 2). A small number of dogs (six) continued to deteriorate beyond the 2-h period after injection, and all died or were sacrificed early. They were all shown at autopsy to be infected with heart worm (*Dirofilaria immitis*). None of the animals included in the final study had heart worm at autopsy.

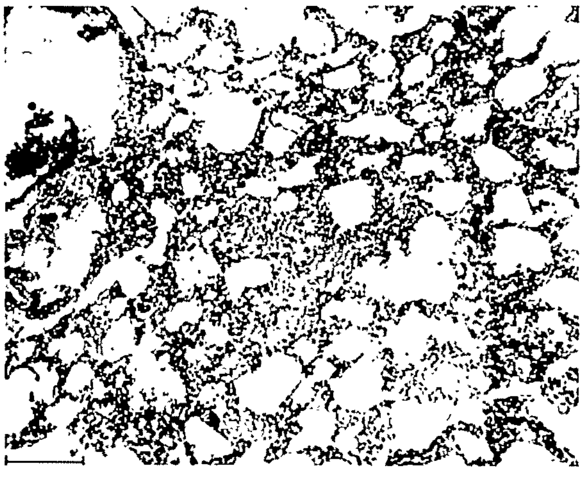

FIG. 2. Lung histology at the completion of the experiments showing pulmonary oedema and cellular infiltrates. Horizontal bar represents 0.1 mm.

The ventilator used in this study has been described previously (Murray Wilson and Baker, 1971). It consists of an electropneumatic converter (Westinghouse Brake and Signal Co. Ltd) which converts the electrical signal from a custom built waveform generator (Childs and Sitch, 1969) into a pressure which is directly proportional to the electrical signal. This pressure is then passed through a metal choke which transduces the pressure directly to flow over a very wide range of pressures, $0-7 \times 10^5\,\mathrm{N\,m^{-2}}$ ($0-100\,\mathrm{lb\,in^{-2}}$). Flow to the patient is further controlled by synchronous control of solenoids in the patient inspiratory/expiratory valve (Baker and Murray Wilson, 1971). The electrical signal has independent control over inspiration and expiration in hundredths of a second up to 5.0 s for inspiration and 6.0 s for expiration. Also there is a patch-board of 20 time-steps during inspiration and 50 amplitude-steps which allows a very wide range of patterns to be constructed. There is a further amplifier down-line from the waveform generator which allows control of tidal volume because it controls the final amplitude of the electrical signal going to the electropneumatic converter. There is a facility to stop the ventilator at any point (either in inspiration or expiration) and hold the solenoid valves closed so that leaks may be tested for, or airways resistance measured (fig. 3).

Anaesthesia was induced in 15 unpremedicated dogs (weight range 24–44 kg) with thiopentone sodium $20-25\,\mathrm{mg\,kg^{-1}}$ injected i.v. A Magill endotracheal tube 9–12 mm i.d. was inserted and the lungs were ventilated with air; gas leaks were tested for in the manner described previously (Baker et al., 1977) by using the inflation hold mode of the ventilator (fig. 3). Anaesthesia was maintained with a mixture of 1% chloralose and 5% urethane warmed to 40°C. Non-depolarizing neuromuscular blockade was produced with pancuronium bromide $0.4\,\mathrm{mg\,kg^{-1}}$ and continued with $0.05-0.1\,\mathrm{mg\,kg^{-1}}$ every 30 min. The frequency of respiration was constant at 15 b.p.m. so that the respiratory cycle time was 4 s, and when inspiratory time changed expiratory time automatically changed as did I:E ratio. The inspiratory flow waveforms used are shown in the figures 4, 5, 6 and 7 which show the generating electrical signal together with the flow and pressure waveforms for reversed ramp, ramp, top-hat and sine waveforms. The inspiratory flow waveforms and times were all selected in a random manner although the top-hat waveform at 1 s (T_I) was used for the initial 2 h following injection of oleic acid. It was also used again at the end of the day's run for comparison of any deterioration with time

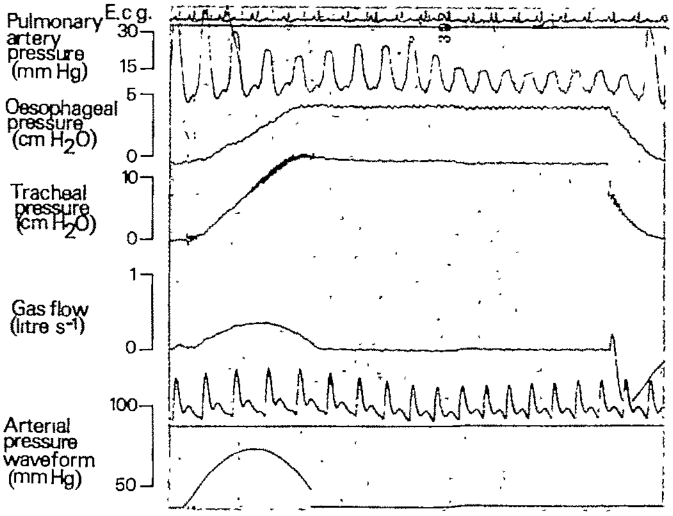

FIG. 3. "Valsalva manoeuvre" carried out to ensure that there was no gas leak from the lungs. This manoeuvre was repeated between all changes of I : E ratio and waveform.

(fig. 1). An initial tidal volume was selected which gave an end-tidal carbon dioxide concentration of approximately 4%. The tidal volume selected was kept constant throughout an experiment and expiration was always passive to atmosphere. The physiological variables studied and the methods used to achieve these have been previously described (Baker et al., 1977). The studies were arranged so that factorial analysis would be used for statistical analysis (Baker et al., 1977).

RESULTS

The histological findings as shown in figure 2 were entirely consistent with pulmonary oedema with alveolar exudates and interstitial oedema, and were similar to those of other studies (Derks and Jacobovitz-Derks, 1977). The statistically significant results are presented in tables I–IV and described graphically in figures 8 and 9 for arterial carbon dioxide tension and airway pressure. The statistical significance is given when better than

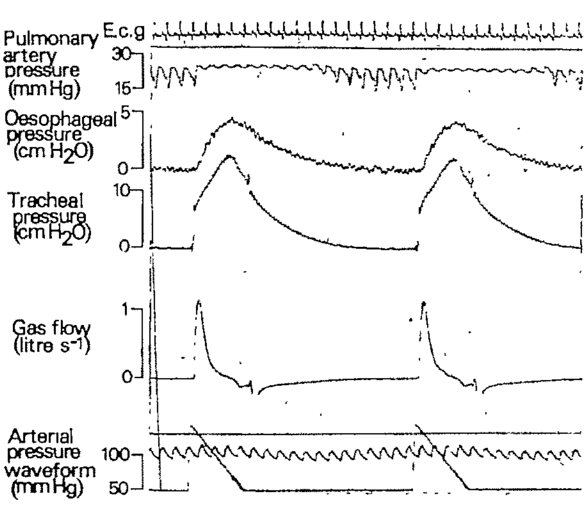

FIG. 4. Experimental recording of the reversed ramp inspiratory flow waveform.

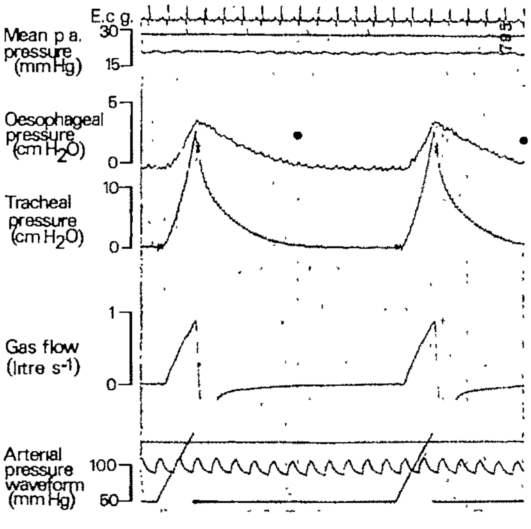

FIG. 5. Experimental recording of the ramp inspiratory flow waveform.

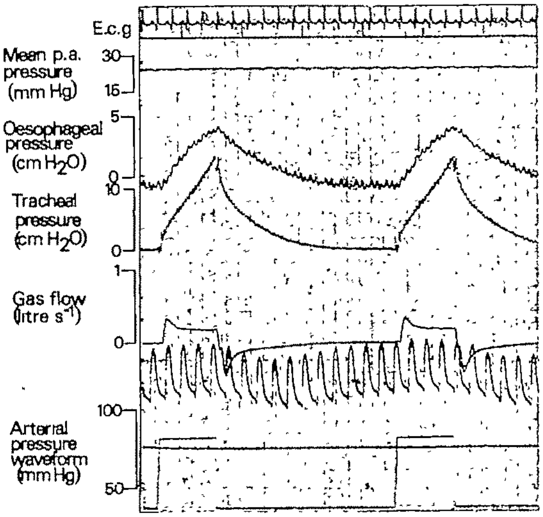

FIG. 6. Experimental recording of the top-hat inspiratory flow waveform.

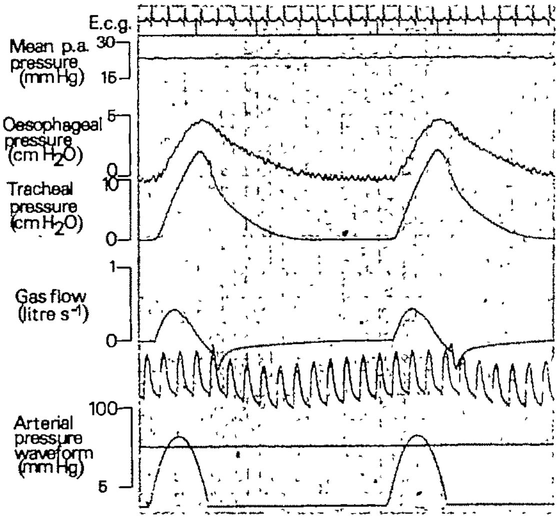

FIG. 7. Experimental recording of the sine inspiratory flow waveform.

$P = 0.05$ and in all cases F values from the analysis of variance had to be significant before comparisons were made. The only physiological variable which was statistically significant for the variations in inspiratory flow waveform and time was Pa_{CO_2}, with which the reversed ramp waveform showed the lowest Pa_{CO_2} and the ramp waveform the highest. For inspiratory time alterations the lowest Pa_{CO_2} was with the longest inspiratory time. There were also statistically significant differences in airway and oesophageal pressures which indicated that there were real variations in the inspiratory flow waveforms and times. There were no statistically significant differences in physiological deadspace to tidal volume ratio (V_D/V_T), dynamic compliance, Pa_{O_2}, ($PA_{O_2}-Pa_{O_2}$), tidal volume, arterial pressure, heart rate, pulmonary artery pressure, body temperature, oxygen consumption or in the duration of the experiments.

DISCUSSION

Many workers (Ashbaugh and Uzawa, 1968; Ehrhart and Hofman, 1981) have shown that i.v. oleic acid in the dog causes a haemorrhagic pulmonary

TABLE I. *Data and statistical significance for Pa_{CO_2} (kPa). The significance table is designed to show the difference between stated means with the statistical significance of that difference. 2.2, 1.0, 0.5 represent inspiratory time in seconds and show the mean values with their standard deviations. RR = reversed ramp; R = ramp; S = sine; T = top-hat inspiratory flow waveforms; SED = standard error of the difference of stated means; d.f. = degrees of freedom of the statistical test; T_{Ia} and T_{Ib} are the compared means of the variable with alteration in inspiratory times, and WF_a and WF_b are the compared means of the variable with alteration in inspiratory flow waveform.* *P <0.05; **P <0.01; ***P <0.001

Inspiratory variable	Mean ± SD	T_{Ib}	T_{Ia} 0.5	T_{Ia} 1.0	WF_b	WF_a RR	WF_a R	WF_a S
Time (s)								
2.2	2.9 ± 0.4	1.0	0.019		R	−0.372***		
1.0	3.3 ± 0.5				S	−0.088	0.284**	
0.5	3.4 ± 0.5	2.2	0.429***	0.409***	T	−0.215*	1.157	0.140
Flow waveform		SED	0.081	d.f. 59		SED 0.094	d.f. 44	
RR	3.1 ± 0.4		Mean 3.219			Synergism +		
R	3.4 ± 0.5							
S	3.1 ± 0.5							
T	3.3 ± 0.4							

TABLE II. *Data and statistical significance for mean airway pressure (cm H_2O). Abbreviations as in table I*

Inspiratory variable	Mean ± SD		T_{1a}			WF_a		
		T_{1b}	0.5	1.0	WF_b	RR	R	S
Time (s)								
2.2	7.58 ± 1.77	1.0	−1.02***		R	2.38***		
1.0	4.61 ± 0.86				S	1.48***	−0.90**	
0.5	3.60 ± 1.27	2.2	−3.99***	−2.97***	T	1.11***	−1.27***	−0.37
Flow waveform			SED 0.25	d.f. 59		SED 0.28	d.f. 44	
RR	6.50 ± 1.68							
R	4.13 ± 1.22		Mean 5.26			Synergism +		
S	5.02 ± 1.26							
T	5.40 ± 1.18							

TABLE III. *Data and statistical significance for mean oesophageal pressure (cm H_2O). Abbreviations as in table I*

Inspiratory variable			T_{1a}			WF_a		
		T_{1b}	0.5	1.0	WF_b	RR	R	S
Time (s)								
2.2	2.23 ± 0.58	1.0	−0.26**		R	0.48***		
1.0	1.50 ± 0.31				S	0.16*	−0.31**	
0.5	1.24 ± 0.38	2.2	−1.00***	−0.74**	T	0.14	−0.34***	−0.03
Flow waveform			SED 0.08	d.f. 59		SED 0.09	d.f. 44	
RR	1.85 ± 0.57							
R	1.38 ± 0.36		Mean 1.66			Synergism +		
S	1.69 ± 0.43							
T	1.71 ± 0.36							

TABLE IV. *Data and statistical significance for pulmonary venous admixture ($\dot{Q}_s/\dot{Q}_t$). Abbreviations as in table I*

Inspiratory variable			T_{1a}			WF_a		
		T_{1b}	0.5	1.0	WF_b	RR	R	S
Time (s)								
2.2	0.324 ± 0.071	1.0	−0.003		R	−0.011		
1.0	0.354 ± 0.074				S	0.014	0.025	
0.5	0.351 ± 0.070	2.2	0.027*	0.030*	T	−0.002	0.013	−0.012
Flow waveform			SED 0.013	d.f. 59		SED 0.015	d.f. 44	
RR	0.344 ± 0.067							
R	0.356 ± 0.081		Mean 0.343			Synergism 0		
S	0.330 ± 0.062							
T	0.342 ± 0.075							

oedema identical with human pneumonopathy —with hypoxia, increased lung water, pulmonary hypertension and reduced lung compliance. Kimura and others (1979) have postulated from their detailed study that the capillary permeability of adult pneumonopathy is caused by endogenous free fatty acids (the same as or similar to oleic acid) released locally in the lung or pulmonary circulation, which injure the alveolar capillary membrane. This mechanism was first postulated by Peltier in 1956.

Early workers used oleic acid doses as high as 0.25 ml kg^{-1} which were rapidly fatal over 1 h, but the standard preparation dose soon tended to become 0.1 ml kg^{-1}, which still caused a progressive deterioration leading to death in approximately 5 h. The dose 0.05 ml kg^{-1} used in this study has now been used by others (0.045 ml kg^{-1} by Ehrhart and

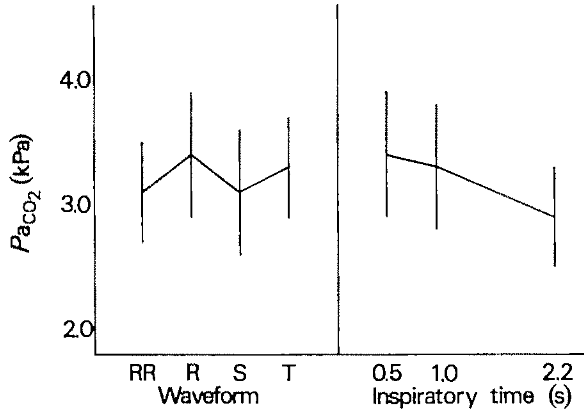

FIG. 8. Changes in means ± SD with different inspiratory flow waveforms and times for Pa_{CO_2}. RR = reversed ramp waveform; R = ramp waveform; S = sine waveform; T = top-hat waveform.

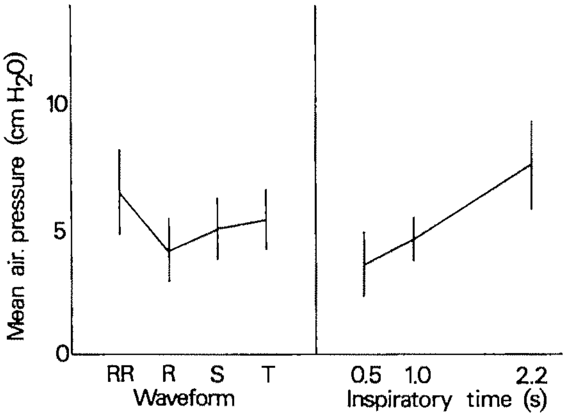

FIG. 9. Changes in means ± SD with different inspiratory flow waveforms and times for mean airway pressure. RR = reversed ramp waveform; R = ramp waveform; S = sine waveform; T = top-hat waveform.

Hofman (1981) and 0.06 ml kg^{-1} by Cheney, Huang and Gronka (1979)) with the production of prolonged stable experimental preparations.

Following the earlier work of Baker and others (1977; Baker, Colliss and Cowie, 1977; Baker, Cowie and Colliss, 1977) it had been expected that the functional differences seen with variations in inspiratory flow waveforms and times would be greater in the pathological state when compared with the normal. However, the present study suggests that instead of increasing the differences with the different inspiratory flow waveforms and times there is a blurring of these differences in the pathological state. The statistically significant differences in mean airway and oesophageal pressures indicate that there were real variations in IPPV (Baker, Colliss and Cowie, 1977). Many other studies which have attempted to look at differences in inspiratory flow waveforms have failed to show significant differences in these pressures, thus showing that their flow waveforms were not dissimilar (Adams, 1970; Adams et al., 1970). From table V it can be seen that mean airway pressure was greatly increased in the oleic acid dogs compared with the normals, presumably because of the decreased lung compliance because of increased lung water.

TABLE V. *Comparison of the means for different physiological variables between the studies on normal animals (Baker, Colliss and Cowie, 1977) and the present study*

Variables	Normal studies	Pulmonary oedema studies
V_D/V_T	0.555	0.566
C_T (ml cm H_2O^{-1} kg^{-1})	1.95	1.87
C_W (ml cm H_2O^{-1} kg^{-1})	5.26	6.99
C_L (ml cm H_2O^{-1} kg^{-1})	3.35	2.72
Pa_{O_2} (kPa)	13.6	8.7
($P_{A_{O_2}} - Pa_{O_2}$) (kPa)	2.2	8.7
Pa_{CO_2} (kPa)	3.7	3.2
$\dot{Q}_D$ (litre min^{-1})	3.39	4.81
$\dot{Q}_F$ (litre min^{-1})	3.53	3.34
MAP (cm H_2O)	3.8	5.26
MOP (cm H_2O)	1.57	1.66
$\dot{Q}_s/\dot{Q}_t$	0.078	0.343

This study showed a rapid early deterioration in Pa_{O_2} which then remained relatively stable over 7 h which agrees with other studies using oleic acid in similar doses. Higher doses lead to progressive deterioration in Pa_{O_2} until death. Pa_{O_2} did not increase with increase in mean airway pressure, a finding of Boros (1979). However, Suter and others (1977) did not find any increase in Pa_{O_2} with an end-inspiratory pause which would have increased the mean airway pressure. Both Boros (1979) and Suter and others (1977) studied patients with the respiratory distress syndrome. Probably results are conflicting from the different studies because of the variation in lung pathology.

In the present study dynamic compliance results were only reduced slightly when compared with the studies on normal dogs (table V) (Baker, Colliss and Cowie, 1977). This apparent small change may have been a result of the different type of animal as the greyhound was used for this study, although Erhardt and Hofman (1981) found only a small decrease in lung compliance despite marked increase in lung water. Although there is a discrepancy between the means for cardiac output measurement in table V, the cardiac outputs as measured by dye dilution and the Fick principle showed a correlation of 0.725 (slope 0.73) which was statistically highly significant ($P<0.001$) and compared very favourably with other cardiac output correlations in the comparison table presented by Baker and colleagues (1977) which was culled from the available literature. There were, however, no significant changes with waveform or time, except for that between inspiratory time 2.2 s and 0.5 s ($P<0.01$) when measured by the Fick principle. There was no corresponding statistical significance when the dye dilution measurement was used. This lack of effect would be predicted from the previous studies by Baker, Colliss and Cowie (1977) where no change was found for different waveforms and times. In the normovolaemic state Morgan, Crawford and Guntheroth (1969) and Sykes and others (1970) have shown that cardiac output is not susceptible to alteration with changes in mean airway pressure.

The present study has shown some small improvement for Pa_{CO_2} with reversed ramp (RR) and sine (S) inspiratory flow waveforms and showed synergism with longer inspiratory times. As increased Pa_{CO_2} can, at times, be troublesome in patients with pneumonopathy there may be some pointers to clinical management in this finding. Changing the inspiratory time, however, had little effect on most variables studied. At 2.2 s inspiratory time the Pa_{CO_2} was significantly smaller, as was $\dot{Q}_s/\dot{Q}_t$. These changes were nevertheless small differences by clinical standards. Why V_D/V_T did not alter significantly with inspiratory changes when Pa_{CO_2} did change is difficult to explain. It would be expected to change similarly; although it did the difference was not statistically significant.

Again from table V an increase in pulmonary venous admixture is shown for the oleic acid studies. This is presumably a result of frank alveolar oedema as shown in figure 2. Because the injury affects the alveolar–capillary membrane without much thrombosis of vessels or capillaries there would not be expected to be much change in V_D/V_T from normal values. Reduction in alveolar deadspace in some alveoli would be balanced by increases in others, along with the accommodation of the tidal volume in a smaller total number of ventilated alveoli. The V_D/V_T ratios are quite high because of the addition of 120 ml of added apparatus deadspace for the pneumotachograph head and solenoid valve.

Overall the impression from this study has been that with pulmonary oedema the physiological derangements are so severe that there are only very small benefits to be gained by modifying the inspiratory flow waveform in IPPV and by changing inspiratory time between 0.5 and 2.2 s.

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QUE SE PASSE-T-IL LORSQU'ON MODIFIE LA FORME DE LA COURBE DE DEBIT INSPIRATOIRE ET LE TEMPS D'INSPIRATION AU COURS D'UNE VENTILATION EN PRESSION POSITIVE INTERMITTENTE: L'OEDEME PULMONAIRE

RESUME

De l'acide oléique a été injecté par voie intraveineuse à des lévriers pour induire un oedème pulmonaire contrôlé. Ensuite ces animaux ont été étudiés en utilisant une ventilation en pression positive intermittente avec quatre formes différentes de courbes de débit inspiratoire, chacune en trois temps inspiratoires différents, pour un cycle respiratoire de durée fixe de 4 s à volume courant constant. Bien qu'il y ait eu des différences statistiquement significatives de pressions dans les voies aériennes et dans l'oesophage entre les différents régimes de débit et de durée de l'inspiration, il y a eu peu de variations des autres paramètres physiologiques étudiés excepté la pression partielle du dioxyde de carbone artériel (Pa_{CO_2}) qui s'est améliorée de façon statistiquement significative avec l'inversion de la pente de débit et avec une courbe de débit sinusoïdale ainsi qu'avec le plus long temps inspiratoire de 2,2 s. Le shunt droit–gauche ($\dot{Q}s/\dot{Q}e$) était également moindre avec le temps inspiratoire le plus long de 2,2 s.

EFECTOS DE LAS FORMAS DE ONDA VARIABLES CORRESPONDIENTES AL FLUJO ASPIRATORIO Y DEL TIEMPO DE LA VENTILACION CON PRESION INTERMITENTE E IMPELENTE: EDEMA PULMONAR

SUMARIO

Se administró ácido oleico intravenoso a galgos para producir edema pulmonar controlado. Estos animales se sometieron a estudio mediante ventilación con presión impelente intermitente (VPII) con cuatro formas de onda aspiratoria diferentes, cada una de ellas a tres tiempos aspiratorios diferentes, siguiendo un ciclo respiratorio fijo de 4 segundos a un volumen de aspiración constante. Aunque había diferencias estadísticas significativas en las presiones de la tráquea y del esófago, entre los diferentes tiempos y formas de onda, hubo pocas variaciones en los otros parámetros fisiológicos estudiados, a excepaión de la tensión arterial del dióxido de carbono (Pa_{CO_2}) que mostró una mejora estadísticamente significativa con entradas de ondas senoidales y pendientes invertidas y, a la larga, tiempos de aspiración de 2,2 segundos. La mezcla venosa ($\dot{Q}_s/\dot{Q}_t$) fue también inferior para los tiempos de aspiración de 2,2 segundos.

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EFFECTS OF VARYING INSPIRATORY FLOW WAVEFORM AND TIME IN INTERMITTENT POSITIVE PRESSURE VENTILATION: EMPHYSEMA

A. B. BAKER, R. RESTALL AND B. W. CLARK

SUMMARY

Emphysema was induced in mongrel dogs by four weekly inhalations of papain. The effects of IPPV were studied using four different inspiratory flow waveforms and each at three different inspiratory times. Tidal volume and respiratory frequency were kept constant and inspiratory time and flow waveform were varied independently. There were statistically significant differences in a number of physiological variables. With a longer inspiratory time of 2.2 s and with the reversed ramp flow waveform V_D/V_T was decreased. With the reversed ramp flow waveform there was a greater total compliance, increased ($P_{AO_2} - P_{aO_2}$) and reduced P_{aCO_2}. There were statistically significant differences in mean airway and oesophageal pressures which indicate valid differences in the flow waveforms and times.

Baker and others (1977), Baker, Colliss and Cowie (1977) and Baker, Cowie and Colliss (1977) have shown that the variation in inspiratory flow waveform and time during IPPV affects physiological variables in the normal dog. Because these differences were not so marked in an experimental model of pulmonary oedema (Baker et al., 1982) another study was carried out on a dog model of pulmonary emphysema to ascertain if there were any influences of flow waveform or time with a different type of lung disease.

Emphysema is one of the commonest chronic pulmonary diseases, and patients suffering from this disease may require IPPV for the treatment of ventilatory failure. Such management is usually not difficult except for weaning, but if a particular method of IPPV were superior this would be an advantage.

There have been a number of reports of pulmonary emphysema produced in different animals following papain inhalation (Gross et al., 1964; Gross et al., 1965; Golding, Greenburg and Ratner, 1968; Park et al., 1969; Cadwell, 1971). The effects of papain inhalation in the dog were first documented by Pushpakom and others (1970), Marco and colleagues (1972) and by D'Angelo (1976). These different studies have shown that the panlobular emphysema produced by papain in dogs is a valid model for the same type of human emphysema (Karlinsky and Snider, 1978).

METHODS

Fifteen mongrel dogs (weight range 18.1–30.8 kg) received weekly inhalations for 4 weeks of 10 ml of nebulized papain in a concentration of 32% (Winthrop Laboratories). These inhalations lasted for 15 min and were administered with a one-way anaesthetic system in a fume cupboard, whilst the animals were anaesthetized and the trachea intubated (fig. 1). No antibiotic was administered to the dogs during this period and they did not have clinical evidence of bronchitis or pneumonia, although all appeared to lack energy by the end of the period of study. One week after the last

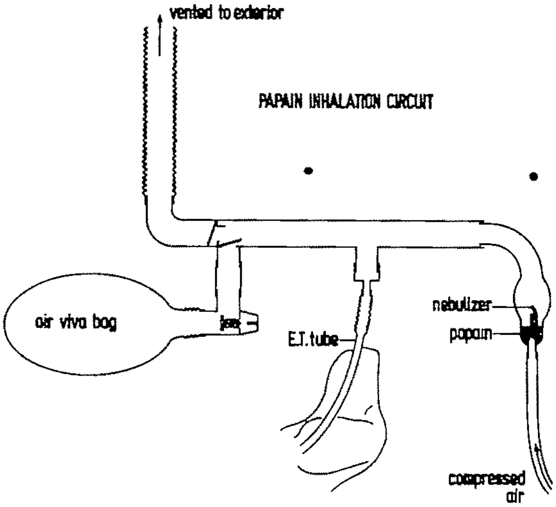

FIG. 1. Schema of the circuit used to nebulize papain into the dogs' lungs. This was done in a fume cupboard to minimize contamination of the environment.

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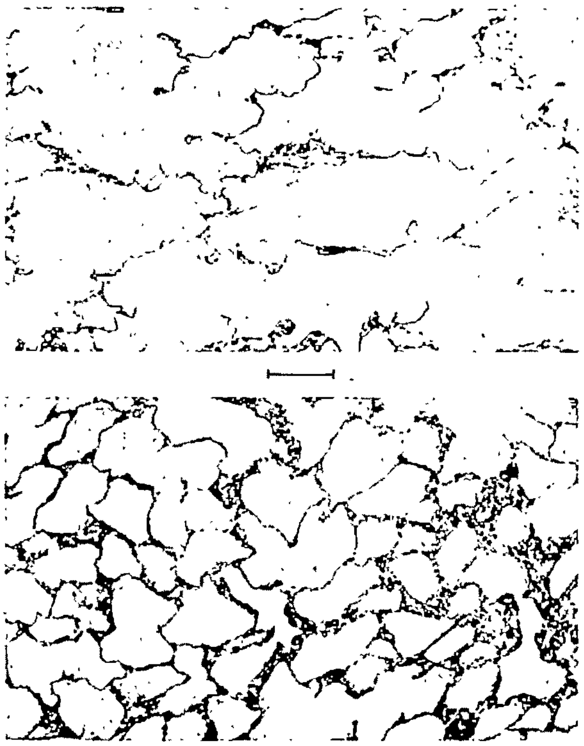

FIG. 2. Lung histology at the completion of an experiment (top); a normal dog's lung tissue is shown below. The normal dog would appear to have some infiltration present, but there is a clear difference in parenchymal structure. Horizontal bar represents 0.1 mm.

inhalation the dogs were studied to determine the effects of altering the inspiratory flow waveform and time in IPPV, using measurement, ventilator and anaesthetic techniques described by Baker and others (1977, 1982). At the completion of the study the lungs were inflated and held in normal inspiration. No further inflation was performed before histological examination of the lungs.

RESULTS

Figure 2 shows the histological appearance of the lungs 1 week after the last papain inhalation. The appearances are consistent with all the previous reports of chronic papain inhalation and indicate that severe emphysema was present.

Tables I–V show the statistically significant results for the various physiological variables. The results are represented graphically in figures 3 and 4 for V_D/V_T and mean oesophageal pressure. The V_D/V_T showed significantly lower values when the reversed ramp flow waveform was used and with a longer inspiratory time. With the reversed ramp waveform there was a statistically significant increase in total dynamic compliance and $(P_{A_{O_2}} - P_{a_{O_2}})$ and a decrease in $P_{a_{CO_2}}$ when compared with other waveforms.

The mean airway pressure and mean oesophageal pressure were significantly different for both waveforms and times and showed synergism. These results provide conclusive evidence that the inspiratory flow waveforms and times were accurately reproduced (Baker, Colliss and Cowie, 1977).

There were no statistically significant differences in dynamic compliance, $P_{a_{O_2}}$, venous admixture $(\dot{Q}_s/\dot{Q}_t)$, tidal volume, arterial pressure, heart rate, pulmonary artery pressure, body temperature, oxygen consumption or the duration of the experiment.

TABLE I. *Data and statistical significance for V_D/V_T (mean ± SD). The significance table is designed to show the difference between stated means with the statistical significance of that difference. 2.2, 1.0, 0.5 represent inspiratory time in seconds and show the mean values with their standard deviations. RR = reversed ramp; R = ramp; S = sine; T = top-hat inspiratory flow waveforms; SED = standard error of the difference of stated means; d.f. = degrees of freedom of the statistical test; T_{Ia} and T_{Ib} are the compared means of the variable with alteration in inspiratory times, and WF_a and WF_b are the compared means of the variable with alteration in inspiratory flow waveform.* *P<*0.05*; **P<*0.01*; ***P<*0.001*

Inspiratory variable	Mean ± SD	T_{Ib}	T_{Ia} 0.5	T_{Ia} 1.0	WF_b	WF_a RR	WF_a R	WF_a S
Time (s)								
2.2	0.679 ± 0.026	1.0	−0.001		R	−0.043***		
1.0	0.695 ± 0.020				S	−0.024***	0.019***	
0.5	0.693 ± 0.018	2.2	0.014**	0.015***	T	−0.037***	0.006	−0.013**
Flow waveform		SED	0.004	d.f. 59		SED 0.005	d.f. 44	
RR	0.663 ± 0.021							
R	0.706 ± 0.024		Mean 0.689				Synergism 0	
S	0.687 ± 0.024							
T	0.700 ± 0.019							

TABLE II. *Data and statistical significance for* $(P_{A_{O_2}} - P_{a_{O_2}})$ *(kPa). Abbreviations as in table I*

Inspiratory variable	Mean ± SD	T_{1b}	T_{1a} 0.5	T_{1a} 1.0	WF_b	WF_a RR	WF_a R	WF_a S
Times (s)								
2.2	3.0 ± 0.6	1.0	−0.033		R	0.359**		
1.0	2.9 ± 0.6				S	0.199	−0.160	
0.5	2.9 ± 0.6	2.2	−0.101	−0.068	T	0.265*	−0.094	0.066
Flow waveform		SED	0.107	d.f. 59		SED 0.124	d.f. 44	
RR	3.1 ± 0.7							
R	2.8 ± 0.5		Mean 2.9				Synergism 0	
S	2.9 ± 0.6							
T	2.8 ± 0.6							

TABLE III. *Data and statistical significance for* $P_{a_{CO_2}}$ *(kPa). Abbreviations as in table I*

Inspiratory variable	Mean ± SD	T_{1b}	T_{1a} 0.5	T_{1a} 1.0	WF_b	WF_a RR	WF_a R	WF_a S
Time (s)								
2.2	3.9 ± 0.3	1.0	−0.091		R	−0.308***		
1.0	3.9 ± 0.3				S	−0.264***	0.044	
0.5	3.9 ± 0.2	2.2	−0.005	−0.086	T	−0.262***	0.046	0.002
Flow waveform		SED	0.049	d.f. 59		SED 0.056	d.f. 44	
RR	3.7 ± 0.3							
R	4.0 ± 0.2		Mean 3.9				Synergism 0	
S	3.9 ± 0.3							
T	3.9 ± 0.2							

TABLE IV. *Data and statistical significance for mean airway pressure* (cm H_2O). *Abbreviations as in table I*

Inspiratory variable	Mean ± SD	T_{1b}	T_{1a} 0.5	T_{1a} 1.0	WF_b	WF_a RR	WF_a R	WF_a S
Time (s)								
2.2	5.80 ± 0.82	1.0	−1.07***		R	2.29***		
1.0	3.49 ± 0.52				S	1.02***	−1.24***	
0.5	2.42 ± 0.42	2.2	−3.38***	−2.31***	T	1.11***	−1.16***	0.09*
Flow waveform		SED	0.11	d.f. 59		SED 0.13	d.f. 44	
RR	5.01 ± 0.80							
R	2.74 ± 0.44		Mean 3.91				Synergism +	
S	3.98 ± 0.59							
T	3.89 ± 0.30							

DISCUSSION

Snider (1981) in a recent Perspective article cited the discovery by Gross and associates in 1964, that papain caused emphysema in animals, as one of the factors which had revolutionized the study of emphysema in the past two decades. He reiterated that such "studies confirmed that papain administered intratracheally or by aerosol consistently produced emphysema".

There has been a general agreement that emphysema is best defined on the basis of morphological changes incorporating alveolar destruction (Thurlbeck, 1977; Karlinsky and Snider, 1978; Guenter, Coalson and Jacques, 1980). The gross and histological appearances of the lungs produced in the present study were typical of panlobular emphysema and agreed with all the previously published studies. Specific functional

TABLE V. *Data and statistical significance for mean oesophageal pressure* (cm H_20). *Abbreviations as in table I*

Inspiratory variable	Mean ± SD	T_{Ib}	T_{Ia}		WF_b	WF_a		
			0.5	1.0		RR	R	S
Time (s)								
2.2	2.36±0.44	1.0	−0.42***		R	0.69***		
1.0	1.50±0.23				S	0.30***	−0.39***	
0.5	1.08±0.18	2.2	−1.28***	−0.87***	T	0.24***	−0.46***	−0.06
Flow waveform		SED 0.06	d.f. 59			SED 0.06	d.f. 44	
RR	1.95±0.40							
R	1.26±0.19		Mean 1.65				Synergism +	
S	1.65±0.27							
T	1.72±0.31							

tests for emphysema such as measurements of FRC, compliance or diffusion capacity were not made during these experiments because Karlinsky and Snider (1978) regarded them as only supplementary to the anatomical studies, and because they have been made by others (Pushpakom et al., 1970; Marco et al., 1972; D'Angelo, 1976). The compliance results obtained previously from normal mongrel dogs (Baker, Colliss and Cowie, 1977) and those from this study are similar. Thus there is no increase in lung compliance with papain-induced emphysema. A similar finding was reported by Marco and others (1972) in dogs and by Caldwell (1971) in rabbits, although both Pushpakom and colleagues (1970) and D'Angelo (1976) found an increase in compliance. This discrepancy was specifically addressed by Karlinsky and Snider (1978) who considered it emphasized the wide range of functional derangement possible with emphysema, and did not in any way invalidate the animal model. The use of 32% papain—a greater concentration than others have used—and repeating treatment over 4 weeks, which others have not done, may have led to greater tissue breakdown of both collagen and elastic elements in the lung parenchyma. Karlinsky and Snider (1978) have shown that an increase in compliance is dependent on elastolytic effects predominating over collagen degradation. However, Osman and others (1980) who have used a plan for introducing papain approaching that used in this study, showed that there was a highly significant reduction in elastin, although this was capable of regeneration with time. V_D/V_T was greater in the dogs with emphysema than in our study of normal dogs, which supports the presence of functional emphysema. Acute models using papain have often yielded lungs infiltrated

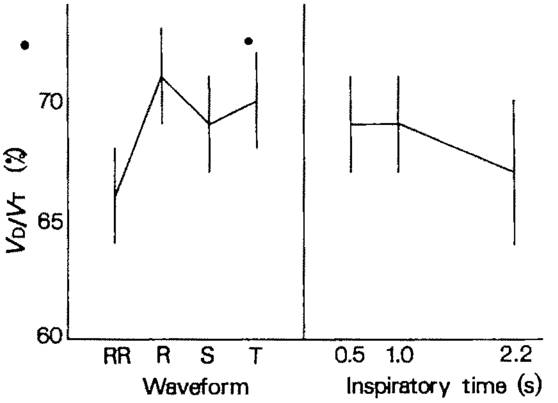

FIG. 3. Changes in means ± SD with different inspiratory flow waveforms and times for V_D/V_T. RR = reversed ramp waveform; R = ramp waveform; S = sine waveform; T = top-hat waveform.

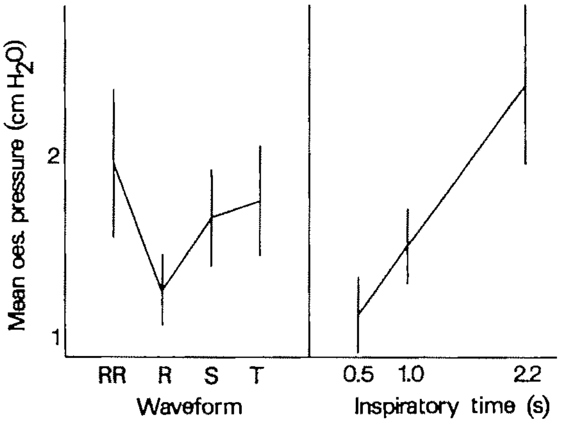

FIG. 4. Changes in means ± SD with different inspiratory flow waveforms and times for mean oesophageal pressure. RR = reversed ramp waveform; R = ramp waveform; S = sine waveform; T = top-hat waveform.

with cells and oedema (Collins, Durnin and Johanson, 1978; Parra, Gaddy and Takaro, 1980) whereas Martin, Daniel and Le Bouffant (1980) have shown that this initial reaction leads in time to gross alveolar septal atrophy and emphysema. This further emphasizes the appropriateness of the method for this present study which allowed the development of gross emphysema as shown histologically.

There was a substantial discrepancy in the mean values of cardiac output measured by dye dilution and the Fick principle (table VI). The linear correlation coefficient was 0.494 (slope 0.476; $P<0.001$). This correlation was the worst in the three studies undertaken with differing waveforms, although it was still within the range of correlations from the literature published in the comprehensive comparative table by Baker and others (1977). It is possible that alveolar destruction with increased $V_\mathrm{D}/V_\mathrm{T}$ upset calculations using the Fick principle by biasing the expired P_O or P_{CO_2} because of rebreathing. There was a significant difference in the dye dilution cardiac output measurement between an inspiratory time of 2.2 s and 1.0 s ($P<0.01$), and 0.5 s ($P<0.05$). This difference was not obtained for cardiac output measurements using the Fick principle.

TABLE VI. *Comparison of the means for different physiological variables in the different studies by Baker, Colliss and Cowie (1977) and Baker and others (1982) and the present studies*

Variables	Normal studies	Pulmonary oedema studies	Emphysema studies
$V_\mathrm{D}/V_\mathrm{T}$	0.555	0.566	0.689
C_T (ml cm H_2O^{-1} kg^{-1})	1.95	1.87	1.65
C_W (ml cm H_2O^{-1} kg^{-1})	5.26	6.99	5.39
C_L (ml cm H_2O^{-1} kg^{-1})	3.35	2.72	2.52
$P\mathrm{a}_{\mathrm{O}_2}$ (kPa)	13.6	8.7	12.6
($P\mathrm{A}_{\mathrm{O}_2} - P\mathrm{a}_{\mathrm{O}_2}$) (kPa)	2.2	8.7	2.9
$P\mathrm{a}_{\mathrm{CO}_2}$ (kPa)	3.7	3.2	3.9
$\dot{Q}_\mathrm{D}$ (litre min^{-1})	3.39	4.81	3.04
$\dot{Q}_\mathrm{F}$ (litre min^{-1})	3.53	3.34	2.05
MAP (cm H_2O)	3.8	5.26	3.91
MOP (cm H_2O)	1.57	1.66	1.65
$\dot{Q}_s/\dot{Q}_t$	0.078	0.343	0.129

$P\mathrm{a}_{\mathrm{O}_2}$ and ($P\mathrm{A}_{\mathrm{O}_2} - P\mathrm{a}_{\mathrm{O}_2}$) were little affected by the severe alveolar destruction. Such good oxygen exchange often occurs in human emphysema when artificial ventilation is required and there is no additional lung problem such as infection. The patient may have poor blood-gas tensions whilst breathing spontaneously, but with the application of IPPV without alteration in inspired oxygen fraction there is a marked increase in $P\mathrm{A}_{\mathrm{O}_2}$ and reduction in $P\mathrm{a}_{\mathrm{CO}_2}$. This is evidence that the major disruption is in the mechanics of ventilation, probably at an alveolar or respiratory bronchiole level.

The results for changes in inspiratory flow waveforms and times show statistically significant differences which are of only minor consequence physiologically. Tables VII and VIII show the statistically significant results of this study compared with previous studies for the normal dogs (Baker, Colliss and Cowie, 1977) and with those for dogs with pulmonary oedema (Baker et al., 1982). Greater variations were obtained in normal dogs

TABLE VII. *Comparison of the studies by Baker and others (1977, 1982) and the present study for inspiratory waveform effect*

Variable	Normal	Pulmonary oedema	Emphysema
$V_\mathrm{D}/V_\mathrm{T}$	RR<S<T & R	=	RR<S<T & R
C_T (ml cm H_2O^{-1} kg^{-1})	RR>S & T>R	=	RR>S & R
C_CW (ml cm H_2O^{-1} kg^{-1})	RR>S & T R>T	=	=
C_L (ml cm H_2O^{-1} kg^{-1})	RR & S & T>R	=	=
$P\mathrm{a}_{\mathrm{O}_2}$ (kPa)	RR>S & T>R	=	=
($P\mathrm{A}_{\mathrm{O}_2} - P\mathrm{a}_{\mathrm{O}_2}$) (kPa)	RR<S & T<R	=	RR>S & T & R
$P\mathrm{a}_{\mathrm{CO}_2}$ (kPa)	RR<S & T<R	RR<R & T S<R	RR<S & T & R
$\dot{Q}_\mathrm{D}$ (litre min^{-1})	RR & T<S & R	=	=
$\dot{Q}_\mathrm{F}$ (litre min^{-1})	RR & T<R T<S	=	=
MAP (cm H_2O)	RR>S & T>R	RR>S & T>R	RR>S & T>R
MOP (cm H_2O)	RR>S & T>R	RR>S & R S & T>R	RR>S & T>R
$\dot{Q}_s/\dot{Q}_t$	RR<S & R S & T<R	=	=

TABLE VIII. *Comparison of the studies by Baker and others (1977, 1982) and the present study for inspiratory time effect*

Variable	Normal	Pulmonary oedema	Emphysema
V_D/V_T	2.2<1.0 & 0.5	=	2.2<1.0 & 0.5
C_T (ml cm H_2O^{-1} kg^{-1})	2.2>1.0 & 0.5	=	=
C_{CW} (ml cm H_2O^{-1} kg^{-1})	=	=	=
C_L (ml cm H_2O^{-1} kg^{-1})	=	=	=
Pa_{O_2} (kPa)	2.2>0.5	=	=
($PA_{O_2} - Pa_{O_2}$) (kPa)	=	=	=
Pa_{CO_2} (kPa)	2.2<1.0 & 0.5	2.2<1.0 & 0.5	=
$\dot{Q}_D$ (litre min^{-1})	=	=	2.2<1.0 & 0.5
$\dot{Q}_F$ (litre min^{-1})	=	2.2<0.5	=
MAP (cm H_2O)	2.2>1.0>0.5	2.2>1.0>0.5	2.2>1.0>0.5
MOP (cm H_2O)	2.2>1.0>0.5	2.2>1.0>0.5	2.2>1.0>0.5
$\dot{Q}_s/\dot{Q}_t$	=	2.2<1.0 & 0.5	=

than in the dogs with emphysema, although the latter showed greater differences than did dogs with pulmonary oedema. While there are statistically significant differences in inspiratory flow waveforms and times, in normal dogs these differences are small and tend to disappear when the lung is severely compromised.

Improvement in respiratory variables is obtained consistently with the reversed ramp waveform and by the longer inspiratory times. The ramp waveform, conversely, produced the poorest results for respiratory variables with very often little difference between the top-hat and sine waveforms effects which are intermediate between those for the other two waveforms. Why this should be is probably closely related to the mean airway pressure relationships, and the mass concentration of gas molecules within the airways and alveoli allowing a longer time for gas exchange to occur, together with better gas distribution throughout the lung. Several of these results are consistent with the findings of Sutter and others (1977), Boros (1979), and of Lindahl (1979) who found improvement in V_D/V_T with increase in mean airway pressure generated by an end-inspiratory pause. Dammann, McAslan and Maffeo (1978) who also increased mean airway pressure with an inspiratory pause did not study V_D/V_T, but found improvements in other respiratory variables. An end-inspiratory pause is akin to the reversed ramp flow waveform used in these studies, and also uses a longer inspiratory time. The effects on dynamic compliance are all consistent even though they are not always statistically significant. Once again the longer time for volume distribution throughout the lungs is probably the major reason for the effects seen. For areas of lung with different time-constants more even ventilation may be achieved, and mean pressures will be less for the same volume. Such waveforms may be of importance in the recovery phase of pneumonopathy when it is common practice to experience tension pneumothoraces because of the patchy recovery from the lung disorder. At such times, the reversed ramp waveform and longer inspiratory times would not be contraindicated because of cardiovascular instability, as the cardiovascular system is usually stable by this stage of the disease. Although changes in $\dot{Q}_s/\dot{Q}_t$ were of no significance generally, the values which did reach statistical significance were consistent and again suggested that reverse ramp waveform and long inspiratory times offered the best results. Such results would be consistent with better overall gas distribution and longer time for molecular exchange within the alveolus.

From the theoretical study by Baker and Hahn (1974) and the practical results from these animal studies, there is the possibility that a negative decreasing exponential inspiratory flow would be the best for respiratory variables, because of the time allowed for gas redistribution within the lung, and also because of the high mean airway pressure. This exponential waveform does, however, require the most inspiratory work at all inspiratory times except for those less than 0.5 s. Such an exponential waveform is very little different from the reversed ramp waveform and was not specifically tested in these studies.

Thus, in terms of clinical usefulness there are possibilities for the improvement of ventilation for patients requiring IPPV, but it must be realized that the statistically significant changes with inspiratory flow waveform and time were small so that only a small improvement in the clinical state can be expected, although in serious illness such a small change for the better may be vital to the eventual outcome for the patient.

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QUE SE PASSE-T-IL LORSQU'ON MODIFIE LA FORME DE LA COURBE DE DEBIT INSPIRATOIRE ET LE TEMPS D'INSPIRATION AU COURS D'UNE VENTILATION EN PRESSION POSITIVE INTERMITTENTE: L'EMPHYSEME

RESUME

Un emphysème a été provoqué chez des chiens batards par quatre inhalations hebdomadaires de papaïne. Les effets de la VPPI ont été étudiés avec quatre différentes formes de courbe de débit inspiratoire, chacune à trois temps d'inspiration différents. Le volume courant (*Vc*) et la fréquence respiratoire étaient maintenus constants et on faisait varier séparément le temps d'inspiration et la forme de la courbe. Il y eut des différences statistiquement significatives de plusieurs variables physiologiques. Avec un temps d'inspiration plus long, de 2,2 s, et avec une inversion de pente de la courbe de débit, le rapport espace mort/*Vc* était diminué. Lorsqu'on inversait la pente de la courbe de débit, la compliance totale était plus grande, la ($P_{OO_2}-Pa_{O_2}$) augmentait et la Pa_{CO_2} diminuait. Il y a des différences statistiquement significatives dans les pressions moyennes des voies respiratoires et de l'oesophage qui traduisent la validité des différences de courbes de débit et de temps d'inspiration.

AUSWIRKUNGEN VERSCHIEDENER FLOWWELLENFORMEN- UND -ZEITEN BEI DER EINATMUNG UND IPP-BEATMUNG AUF EMPHYSEME

ZUSAMMENFASSUNG

An Bastardhunden wurde durch 4 Papain-Inhalationen in der Woche ein Emphysem induziert. Wir untersuchten die Auswirkungen von IPPB, indem wir vier verschiedene inspiratorische Flowwellenformen mit je 3 verschiedenen Inspirationszeiten anwandten. Das Atemzugvolumen und die Atemfrequenz wurden konstant gehalten, aber wir veränderten die Atemzeit und die Flowwellenform unabhängig voneinander. Es gab statistisch signifikante Unterschiede bei einer Anzahl von physiologischen Variablen. Mit einer längeren Einatemzeit von 2,2 s und umgekehrten rampenförmigen Flowwellen nahm das Verhältnis von Totraumvolumen zu Atemzugvolumen ab. Mit der umgekehrten Rampen-Flowwellenform war die totale Compliance grösser, nahm $(P\text{A}_0-P\text{a}_{O_2})$ zu und $P\text{a}_{CO_2}$ ab. Es gab statistisch signifikante Unterschiede der mittleren Drucke in den Luftwegen und im Ösophagus, die auf wichtige Unterschiede in den Flowwellenformen-und-zeiten hinweisen.

EFECTOS DE FORMAS DE ONDA DEL FLUJO ASPIRATORIO VARIABLES EN FUNCION DEL TIEMPO EN LA VENTILACION DE PRESION IMPELENTE INTERMITENTE: ENFISEMA

SUMARIO

Se indujo enfisema en perros callejeros mediante inhanalaciones semanales, efectuándose cuatro de ellas. Se analizaron los efectos de la VPII de cuatro formas de onda diferentes de flujo aspiratorio y, cada una de ellas, en tres tiempos aspiratorios diferentes. El volumen aspiratorio y la frecuencia respiratoria se mantuvieron constantes y el tiempo de aspiración y la forma de onda del flujo se variaron de independientemente. Hubo diferencias estadísticas significativas en un cierto número de variables fisiológicas. La relación V_D/V_T disminuyó al aumentarse el tiempo de aspiración a 2,2 segundos y con las formas de onda de flujo con pendiente inversa. Con las formas de onda de flujo con pendiente inversa se obtuvo una mayor conformidad total, una mayor $(P\text{A}_{O_2}-P\text{aO}_2)$ y una $P\text{a}_{CO_2}$ reducida. Hubo diferencias estadísticas significativas en las presiones medias del esófago y de la tráquea, lo que indica diferencias válidas en los tiempos y en las formas de onda del flujo.

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HALOTHANE ADSORPTION COMPLICATING THE USE OF SODA-LIME TO HUMIDIFY ANAESTHETIC GASES

W. K. GRODIN AND R. A. EPSTEIN

SUMMARY

If the anaesthetic circle system is arranged to increase the humidity of fresh anaesthetic gases by placing the carbon dioxide absorbent canister between the fresh gas inlet and the patient, drying of the soda-lime can occur. Very dry soda-lime adsorbs significant quantities of halothane. Using fresh soda-lime, effluent halothane concentration reached 50% of the input concentration in 35 s, but this time increased to 500 s when dry soda-lime was used. The use of dry soda-lime can result in a slow inhalation induction or in the release of adsorbed halothane during a subsequent anaesthetic.

Adequate humidification of inspired gas has been recognized as a significant problem in clinical anaesthesia (Spalding, 1956; Burton, 1962), especially with paediatric patients (Rackow and Salanitre, 1969). A common solution is to add a humidifier to the fresh gas line or to the inspiratory limb of the circle. Déry and others (1967) and Berry and Hughes-Davies (1972) described a paediatric anaesthesia circuit which delivered from the soda-lime itself 80% relative humidity at 24 °C. They achieved this by placing the soda-lime canister between the source of fresh gas and the patient, allowing the dry gas to take up water from the absorbent. No serious problems have been reported using this arrangement.

Using a similar circle (fig. 1, right), we noted that occasionally the induction of anaesthesia with halothane was markedly prolonged. We suspected this was caused by adsorption of halothane on to the soda-lime. Eger, Larson and Severinghaus (1962), using fresh soda-lime (15% water by weight), showed that for halothane the soda-lime/air partition coefficient is about 1, suggesting that halothane uptake is negligible. However, Titel and others (1968) and Lowe, Titel and Hagler (1971) reported that halothane is taken up by soda-lime as an inverse function of the water content of soda-lime. If the soda-lime is used to humidify fresh gas, then the soda-lime must dry, allowing halothane to be adsorbed. We investigated whether the use of this anaesthesia circle configuration could produce sufficient drying of the soda-lime to result in a clinically significant adsorption of halothane.

METHODS

Drying of soda-lime and distribution of remaining water. Four twin-compartment absorbent canisters were each filled with 2.3 kg of fresh soda-lime (Sodasorb, W. R. Grace and Co., confirmed 14–16% water by weight, 4–8 mesh). They were placed in the anaesthesia circle as shown in figure 1 (right), and exposed to a flow of dry oxygen 5 litre min^{-1} for 30 or 40 h. The fractional water content of the soda-lime in two canisters was then determined by calculating the change in weight produced by drying them for 3 h in a 120 °C kiln. The distribution of water within a canister was determined by studying six 50-g samples of soda-lime from various sites within the upper (proximal) and the lower (distal) compartments of each of the remaining two canisters. The water content of each sample was determined as above.

Adsorption of halothane by soda-lime. The adsorption of halothane by soda-lime was studied by measuring changes in halothane concentration at a point between the outlet of the canister and the rubber breathing hose in the paediatric circle described above. A 5-litre min^{-1} flow of 1% halothane was introduced to the circle via the fresh gas inlet. No known absorbent, such as rubber, was used in the apparatus. The soda-lime had been pretreated by passing through it a 5-litre min^{-1} flow for 0–40 h

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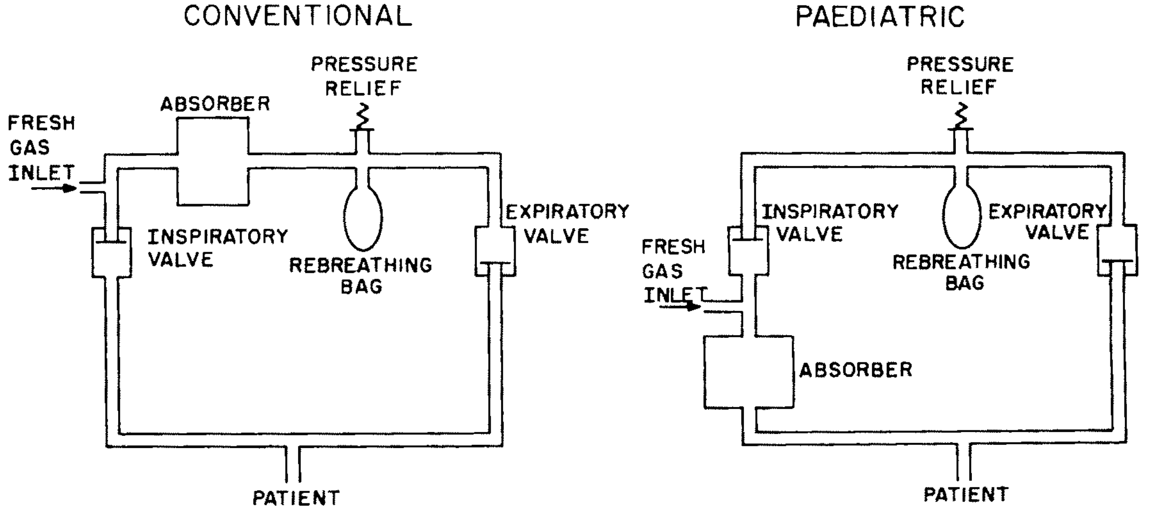

FIG. 1. Left: Conventional circle showing the source of fresh gas (at arrow) placed after the soda-lime canister and before the inspiratory valve. Right: Paediatric circle designed to provide humidification, showing source of fresh gas (at arrow) placed after the inspiratory valve and before the soda-lime canister.

of (a) dry oxygen, (b) oxygen saturated with water vapour at ambient temperature or (c) dry oxygen for 40 h and then, for an additional 40 h, a 5-litre min^{-1} flow of oxygen saturated with water vapour at 37 °C. Halothane concentration was measured using an infra-red analyser (Beckman LB-2) calibrated at four points with halothane standards (Matheson Gas Products) and recorded on a polygraph (Offner). The time required for the effluent halothane concentration to reach 50% of the fresh gas concentration was determined from the polygraph trace and termed t_{50} (fig. 2). When effluent halothane concentration was greater than 95% of the halothane concentration at the fresh gas inlet, halothane input was discontinued and the adsorbed halothane was washed out by continuing the 5-litre min^{-1} flow of dry oxygen.

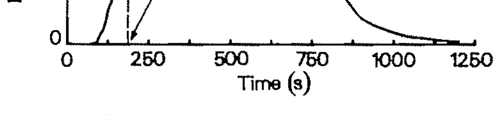

FIG. 2. t_{50} is defined as the time at which halothane concentration at the absorber exit equals half the concentration at the absorber inlet. The initial phase of the sigmoid-shaped curve indicates that a clinically significant period of time passes before any halothane can be detected in the effluent gas.

Halothane adsorption by "clinical" soda-lime. Canisters of soda-lime were collected from three circuits where the anaesthetists reported that an inhalation induction was markedly prolonged, and stored in double polythene bags. All patient records were analysed for other potential sources of prolongation, such as difficulty in airway management, inadequate flows or low halothane concentrations. Previous usage of these canisters of soda-lime was unknown. In each case, adsorbed halothane was washed out for a minimum of 10 min until no effluent halothane could be detected when oxygen was passed through the circle. t_{50} was determined and the washout curve plotted for each specimen, as in the previous experiment.

RESULTS

Drying of soda-lime and distribution of remaining water. The water content of the soda-lime exposed to dry oxygen for 30 h was 9.0% while that of the soda-lime exposed for 40 h was 6.8%. The water contents of 50-g samples of soda-lime were variable. After exposure to dry oxygen 5 litre min^{-1} for 30 h, the water contents in the proximal canister ranged from 3 to 5% while that of the distal canister ranged from 9 to 11%. After 40 h exposure, the water contents ranged from 0.1 to 4% and 7 to 11%,

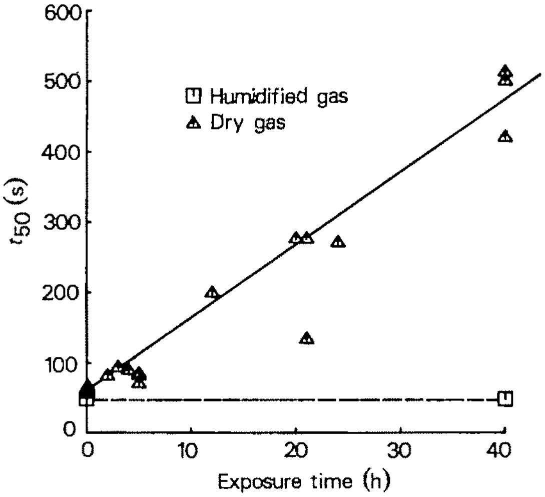

FIG. 3. t_{50} increases if the soda-lime has been exposed to drying gases. The delay is approximately 500 s after 40 h of exposure. Exposure to humidified gas does not increase t_{50}. The solid line represents the best linear fit ($r = 0.97$).

respectively. Thus, soda-lime around the fresh gas inlet became dry while the remainder of the canister of soda-lime retained most of its water content.

Adsorption of halothane by soda-lime. Figure 2 is representative of the sigmoid-shaped curve of the effluent halothane concentration plotted against time. t_{50} values for different soda-lime pretreatment programmes are plotted in figure 3. Fresh soda-lime not exposed to drying gas, had a mean t_{50} of 38 s (range 33–40 s). t_{50} increased linearly with duration of exposure to dry oxygen ($r = 0.97$), reaching 500 s after 40 h of drying (range 430–525 s). Soda-lime treated with humidified oxygen for 40 h, with or without pretreatment with dry gas, had the same t_{50} as fresh soda-lime. The washout curve was also found to be sigmoid and is illustrated in figure 2. Washout of fresh soda-lime to 0.05% effluent halothane required a mean washout time of 88 s (range 80–95 s). Soda-lime exposed to dry oxygen for 40 h had a mean washout time of 1250 s (range 1100–1600 s). Washout time for soda-lime exposed to humidified oxygen, or which was exposed to dry and then humidified oxygen was the same as for fresh soda-lime.

Halothane adsorption by "clinical" soda-lime. t_{50} values of soda-lime from circuits where an inhalation induction had been markedly prolonged averaged 450 s, with a range of 345–650 s. The washout time to 0.05% effluent halothane concentration averaged 1050 s (range 900–1300 s). The adsorption–washout plot had the same sigmoid shape as that found in experiments with dry soda-lime.

DISCUSSION

The use of dry gas during anaesthesia has been associated with V/Q abnormalities and increased microatelectasis (Rashad et al., 1976), loss of body heat (Roe, Santulli and Blair, 1966; Rashad and Benson, 1967), adnormalities of ciliary morphology and function (Chalon, Loew and Malebranche, 1972), and an increase in viscosity of mucus, crust formation and obstruction of the respiratory tree or endotracheal tube (Spalding, 1956). To avoid these problems, fresh gases are usually passed through a humidifier before delivery to the patient. Humidifiers, however, are an added expense, take up important space around paediatric patients, and have hazards of their own (Egan, 1973).

Since Déry and others (1967) and Berry and Hughes-Davies (1972) described the use of soda-lime as a humidifier by passing fresh gas first through the canister before delivery to the patient, an elegant and inexpensive technique has been available for clinical use. An improvement in this circle is described by Chalon, Simon and others (1978) who recently constructed a circle which uses not only the water of the soda-lime but also the heat of reaction from the canister to maximize humidification. A disposable canister circuit is also commercially available (Disp CO2 Sorb, Dryden Corporation) which uses the humidification capacity of soda-lime (Weeks, 1975).

Few disadvantages have been attributed to such circles (fig. 1, right). When gas composition is altered, a minor lag time may be expected as the void space is washed out (Schreiber, 1972). Chalon (1974) has pointed out the possibility of bacterial growth on a warm, moist inspiratory valve, which may also cause valve malfunction. It has also been suggested that additional modifications of the circle may be desirable to augment humidification further (Ramanathan, Chalon and Turndorf, 1976; Chalon, Patel et al., 1978; Chalon, Simon et al., 1978). However, in this study we have demonstrated a major deficiency. We have shown: (1) exposure of soda-lime to a flow of dry gas results in drying of the soda-lime; (2) the soda-lime in the proximal canister becomes relatively dry when that in the distal canister still contains large amounts of water. Thus, clinically significant quantities of halothane can be adsorbed. This occurs at a time when the effluent gas continues to be well-humidified (Salanitre, E., personal communication); (3) halothane adsorption increases with drying time; (4) adsorbed halothane can subsequently be slowly released; (5) soda-lime recovered from three circuits where induction was unexpectedly prolonged was later found to adsorb large amounts of halothane.

Soda-lime in this anaesthesia circuit dries under two common clinical conditions. When a patient is disconnected from the circle, and the flow of gas through the circle is inadvertently continued, drying will occur. If the flow is not stopped at the end of the working day, a significant drying will have occurred by morning, producing in the soda-lime the capacity to adsorb a clinically significant quantity of halothane. Drying will also occur when the flow of fresh gas greatly exceeds minute ventilation, although it is doubtful whether this often leads to a clinically significant change.

Clinical problems can follow the use of dry soda-lime. Since t_{50} increases about 10 s for each hour of exposure to dry gases, an inhalation induction can be markedly slowed, leading to a prolonged excitement phase. A patient who is anaesthetized using an anaesthesia circle containing soda-lime that has adsorbed halothane will receive this agent as it is being washed out from the soda-lime by fresh gas. This presents a potential danger to a patient for whom halothane is contraindicated. A patient at risk from malignant hyperpyrexia is probably not sufficiently protected from halothane exposure by changing only the rubber components of the circle (Eger, Larson and Severinghaus, 1962); the soda-lime must be changed as well.

Despite these problems, a circuit which utilizes the water content of soda-lime to humidify anaesthetic gases is useful in paediatric anaesthesia. However, it may be advantageous to modify the circuit so that, during induction, fresh gas enters the inspiratory limb after the canister, thus delivering a known halothane concentration directly to the patient. Once a suitable depth of anaesthesia is attained, the source of the fresh gas can be switched to a site before the canister, allowing humidification of the fresh gas for the duration of the anaesthetic.

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ADSORPTION D'HALOTHANE COMPLIQUANT L'UTILISATION DE CHAUX SODEE POUR HUMIDIFIER LES GAZ ANESTHESIQUES

RESUME

Si le circuit anesthésique est conçu pour augmenter l'humidité des gaz anesthésiques frais en plaçant la boîte absorbant le dioxyde de carbone entre l'arrivée des gaz frais et le patient, il peut s'ensuivre un assèchement de la chaux sodée. La chaux sodée très sèche adsorbe des quantités significatives d'halothane. Si l'on utilise de la chaux sodée fraiche, la concentration d'halothane à la sortie du canister atteint 50% de la concentration à l'entrée en 35 s, mais ce temps s'allonge jusqu'à 500 s lorsqu'on utilise de la chaux sodée sèche. L'utilisation de chaux sodée sèche

peut entraîner un allongement du temps d'induction par inhalation ou le relargage de l'halothane adsorbé au cours d'une anesthésie ultérieure.

DURCH BINDUNG VON HALOTHAN AUFTRETENDE KOMPLIKATION BEI DER BENUTZUNG VON ABSORBERKALK SUR ANFEUCHTUNG DER NARKOSEGASE

ZUSAMMENFASSUNG

Wenn im Kreissystem des Narkosegerätes der CO_2-Absorberbehälter zur Anfeuchtung der Narkosegase zwischen dem Frischgaseinlaß und dem Patienten angeordnet ist, kann der Absorberkalk austrocknen. Sehr trockener Absorberkalk nimmt deutliche Mengen von Halothan auf. Bei der Benutzung von frischem Absorberkalk erreichte das ausströmende Halothan nach 35 s 50% der Konzentration des zugemischten Halothans, während sich diese Zeit bei Verwendung von trockenem Absorberkalk auf 50 s verlängerte. Die Benutzung von trockenem Absorberkalk kann das Einsetzen der Inhalationsnarkose verlangsamen oder dazu führen, daß absorbiertes Halothan bei weiteren Narkosen freigesetzt wird.

COMPLICACION DEL USO DE LA CALIZA SODICA PARA HUMIDIFICAR LOS GASES ANESTESICOS COMO CONSECUENCIA DE LA ABSORCION DE HALOTANO

SUMARIO

Si el sistema del ciclo anestésico se dispone para aumentar la humedad de gases anestésicos puros, colocando el filtro absorbente de dióxido de carbono entre la entrada de gas puro y el paciente, puede llegar a secarse la caliza sódica. Cuando ésta está muy seca absorbe cantidades importantes de halotano. Haciendo uso de caliza sódica pura, la concentración de halotano de salida alcanzó el 50% de la concentración de entrada en 35 s, pero este tiempo llegó a ser de 500 s cuando se usó caliza sódica seca. El usar caliza sódica seca puede traer como consecuencia una lenta inducción de aspiración o la liberación de halotano absorbido durante una anestesia posterior.

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MECHANISMS OF HALOTHANE ADSORPTION BY DRY SODA-LIME

W. K. GRODIN, M. A. F. EPSTEIN AND R. A. EPSTEIN

SUMMARY

Using fresh soda-lime (15% water by weight) the soda lime/air partition coefficient of halothane was found to decrease as a function of vapour phase halothane concentration from 2.40 at 0.3% halothane by volume to 1.15 at 2.6%, but adsorption generally followed Henry's law. However, soda-lime dried to a constant weight and subsequently exposed to various concentrations of halothane adsorbed approximately 320 μlitre of vaporized liquid halothane per 100 g before a measurable concentration of halothane was detected in the vapour phase. Adding additional halothane then caused a linear increase in vapour concentration. We conclude that dry soda-lime can adsorb large quantities of halothane by a mechanism which is similar to that of a molecular sieve. After these "high affinity" sites are satisfied, additional halothane is adsorbed by a mechanism following Henry's law.

We have shown recently that the use of soda-lime to humidify anaesthetic gases in a circle system can cause drying of the soda-lime (Grodin and Epstein, 1982). This is significant because dry soda-lime can adsorb large amounts of halothane, which can slow an inhalation induction. Conversely, adsorbed halothane can be released to a flow of fresh gas subsequently introduced to the circle. We have investigated the effect of the water content of soda-lime on the partition of halothane between that adsorbed on soda-lime and that remaining in the vapour phase to determine the mechanism of halothane adsorption.

METHODS

Pretreatment of soda-lime. Soda-lime (Sodasorb, WR Grace & Co., indicating soda-lime, 4–8 mesh) with various water contents was used. We confirmed the manufacturer's specification that "fresh" soda-lime contains 14–16% water by weight baking it in a 120 °C kiln to a constant weight and measuring the fractional weight loss. "Dry" soda-lime was prepared by placing samples in the 120 °C kiln for 3 h and allowing it to cool in a desiccator.

Experimental apparatus and programme. An equilibration chamber was constructed from a glass 500-ml Erlemeyer flask (total volume 600 ml ± 1 ml). A Luer fitting for the attachment of a three-way nylon stopcock was built into a side wall. A glass evaporation tray was set inside the flask just below the Luer fitting. A glass cap with a Teflon sleeve sealed the top of the flask and was held in place by rubber bands attached to hooks moulded into the cap and walls. The volume of the flask was determined by weighing before and after filling it with water. Preliminary studies showed that the concentration of halothane mixtures placed in this system changed less than 0.01% over 48 h. Weighed samples (100 g ± 0.5 g) of fresh or dry soda-lime were placed on the chamber floor using a glass funnel with the stem bent to curve around the evaporating tray. This avoided contact between the soda-lime and subsequently added liquid halothane. Air was aspirated from the middle port of the three-way stopcock to develop a partial vacuum within the chamber. The needle of a microlitre syringe (Hamilton) was passed through a self-sealing membrane mounted on the stopcock and a measured quantity of liquid halothane was injected. Ten to 500 μlitre was used to produce vapour concentrations up to 2.5%. After evaporation was complete, air was admitted through the stopcock to return the chamber to ambient pressure. Twenty-four hours were allowed for equilibration. Duplicate 2-ml samples of vapour from the chamber were obtained using a glass syringe and analysed using a Beckman LB-2 infra-red gas analyser calibrated at four points with

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TABLE I. *Symbols*

Cv	= Concentration of halothane in vapour phase (%)
Dl	= Density of liquid halothane = 1.86 g ml^{-1}
Ds	= Density of soda-lime = 1.96 g ml^{-1} fresh 2.21 g ml^{-1} dry
MV	= Molar volume = 22.4 litre, STP
MW	= Molecular weight of halothane = 197.4
P	= Partition coefficient
Q	= Quasipartition coefficient
S	= Weight of soda-lime (g)
*V**	= Maximal *Vi* which produces *Cv* = 0 (μlitre)
Vf	Volume of flask = 600 ml
Vi	Volume of liquid halothane injected (μlitre)

halothane vapour of known concentration (Matheson Gas Products). A total of 68 experiments were performed. All experiments were conducted at room temperature (22–24 °C).

Data analysis. It can be shown that, if the relationship between the volume of liquid halothane injected (*Vi*) and the vapour phase concentration of halothane (*Cv*) is linear and passes through the origin, Henry's law applies. From the definition of the partition coefficient (*P*) based on Henry's law (Larson, Eger and Severinghaus, 1962):

$$P = \frac{\text{vol of agent adsorbed/vol of adsorbent}}{\text{vol of agent in vapour phase/vol of vapour phase}} \qquad (1)$$

Substituting experimental values (Brown, 1958; Larson, Eger, and Severinghaus, 1962):

$$P = \frac{(Vi\,Dl\,MV/MW) - Cv[Vf - (S/Ds)]}{(S/Ds)Cv} \qquad (2)$$

This can be rearranged to give an expression for *Cv* as a function of *Vi*.

$$Cv = \left\{ \frac{Dl\,MV/MW}{P(S/Ds) + [Vf - (S/Ds)]} \right\} Vi \qquad (3)$$

If the term within the brackets is constant, this is the equation of a straight line passing through the origin. This will be the case if *P* is constant. Since a least-square fit is the most efficient way to estimate the slope of such a line (Brownlee, 1965), it is reasonable to derive the partition coefficient from the slope when dealing with real data which may include random errors. In addition, the estimate of the partition coefficient obtained from the slope of a regression line is probably better than that which could have been obtained by simply averaging the partition coefficients determined at each concentration from the same data as the slope has the smallest variance of all unbiased linear estimators (Brownlee, 1965). Setting the expression within the brackets in equation (3) equal to the estimated slope, *b*, it can be shown that:

$$P = \frac{(Dl\,MV/MW) - b[Vf - (S/Ds)]}{b(S/Ds)} \qquad (4)$$

For a system in which the *Cv*– *Vi* data are linear for all non-zero values of *Cv*, but where there is a positive *Vi* intercept, a parameter can be derived which we call the quasipartition coefficient, *Q*, from the slope of this linear segment. If the *Vi* intercept is *V**, then:

$$Cv = \left\{ \frac{Dl\,MV/MW}{Q(S/Ds) + [Vf - (S/Ds)]} \right\} (Vi - V^{*}) \qquad (5)$$

and using the form $Cv = g(Vi - V^{*})$:

$$Q = \frac{(Dl\,MV/MW - g[Vf - (S/Ds)]}{g(S/Ds)} \qquad (6)$$

Thus, if a linear fit is possible, *V** may be identified with an initial "fully adsorbed" quantity of halothane and *Q* identified as the partition coefficient describing a second and distinct adsorption process. For those systems which follow Henry's law at all times, the line passes through the origin, that is, $V^{*} = 0$, and $Q = P$.

In preliminary experiments with fresh soda-lime, we found that *Cv* invariably increased with increasing *Vi*. With dry soda-lime, however, no halothane could be detected in the vapour phase until a critical *Vi* had been injected. Thereafter, *Cv* increased in an apparently linear fashion. We first plotted *Cv* as a function of *Vi* and then attempted to fit linear and higher order functions to the data. A higher order regression was not considered necessary because it decreased the sum of the squares of the deviation from the regression line by less than 1%. Only those points with *Cv* greater than zero were used in fitting the regression line. *Q* was then calculated from the slope. The *Vi* intercept, *V**, was calculated as the quotient of the *Cv* intercept and the slope, and its 95% confidence limit was estimated (Brownlee, 1965). Finally, Student's *t* tests were used to evaluate differences in the value of *P* at different values of *Vi*.

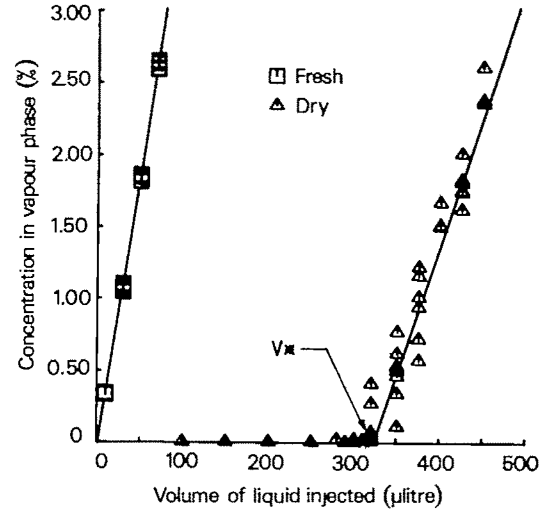

FIG. 1. Concentration of halothane in vapour phase (*Cv*) (%) plotted as a function of the volume of liquid halothane injected (*Vi*) (µlitre) for fresh and dry soda-lime. Data points and regression lines are plotted. Both regression lines have statistically significant *x*-intercepts. Note that *V** for dry soda-lime is very large.

RESULTS

Figure 1 shows *Cv* plotted as a function of *Vi*. The correlation coefficients are 1.00 and 0.97 for fresh and dry soda-lime, respectively.

(A) *Fresh soda-lime.* The regression line has a small but significantly positive *Vi* intercept. *V** is equal to 1.52 (±0.40) at the 95% confidence level) and the slope equals 0.0380 ± 0.0002 (SD). *Q*, calculated from the slope, is equal to 1.12. We calculated the value of the mean value of *P* for each of the four values of *Vi* and found that *P* is greatest at the smallest *Cv* and decreases as *Cv* increases (table II). The range is 1.15 to 2.40.

TABLE II. *Partition coefficient for fresh soda-lime at various volumes of injectate*

Vi (µlitre)	Mean *Cv* (%)	*P* (mean ± SD)	No.
10	0.34	2.40 ± 0.20	6
30	1.06	1.85 ± 0.14	8
50	1.85	1.36 ± 0.13	6
70	2.61	1.15 ± 0.11	8

(B) *Dry soda-lime.* Inspection of a plot of *Cv* as a function of *Vi* shows that a large amount of halothane must be added before any halothane is detected in the vapour phase. The regression line has a large and significantly positive *Vi* intercept. *V** is equal to 317.9 (±5.9 at the 95% confidence limit) and the slope equals 0.0174 ± 0.0008 (SD). The slope for dry soda-lime is significantly less than that for fresh soda-lime ($P < 0.001$). *Q*, calculated from the slope, is equal to 17.7. Since *V** is very large the partition coefficient was not calculated for each of the values of *Vi*.

DISCUSSION

We have shown that adsorption of halothane by soda-lime is a function of the water content of the soda-lime and demonstrated that this adsorption is biphasic. Initially, all halothane is extracted from the vapour phase and bound to soda-lime, but after the adsorption of *V** of halothane, adsorption becomes a function of the vapour phase halothane concentration. Eger, Larson and Severinghaus (1962) have previously shown that fresh soda-lime (15% water by weight) has a partition coefficient of about 1, which we have confirmed. Titel and others (1968) state, without presenting data, that the uptake of halothane by soda-lime increases logarithmically with decreasing water content of the soda-lime. Although we cannot confirm that the relationship is logarithmic, we have also found that as the water content of the soda-lime decreases, its capacity to adsorb halothane increases.

The partition coefficient is useful for describing the relationship between the concentration of a substance in two phases at equilibrium. For many systems, the partition coefficient is independent of concentration. In such cases, Henry's law applies and a single parameter describes the physical relation. However, many real systems do not follow Henry's law in a simple fashion and it is useful to analyse such data with techniques which will emphasize the relationship to a postulated physical model. One hypothesis that should be considered is that the partition coefficient itself actually changes with concentration. This might occur if the adsorption process alters the nature of the absorbent, as when ether dissolves in blood (Eger, Shargel and Merkel, 1963). For this purpose, it is proper simply to describe the partition coefficient as a continuously changing function of vapour phase concentration. However, it is also possible that two or more different mechanisms are simultaneously operating, one of which is quantitatively more important under some specific condition. A sharp break in the *Cv*–*Vi* curve may suggest this latter possibility and analysis of the components of the curve may identify the nature of these mechanisms.

Other deviations from Henry's law have been reported in connection with anaesthetic agents. The dependence of the blood/gas partition coefficient on concentration has been reported at low concentrations of cyclopropane (Gregory and Eger, 1968) and at high concentrations of ether (Cowles, Borgstedt and Gillies, 1971). However, as long as the partition coefficient is measured at all relevant anaesthetic concentrations, sufficient data are provided for the predicition of uptake and distribution.

In order to understand why the partition coefficient for a particular system is not constant, it is necessary to consider the relation as a whole. In the case of fresh soda-lime, a small but statistically significant variation in the value of *P*, from 1.15 to 2.40, was found. This might be explained by at least three hypotheses. The decreasing *P* with increasing *C*v might result from the extremely uneven surface of the porous crystalline soda-lime granule becoming coated by halothane molecules in a series of layers, the surface area decreasing as the adsorbed halothane "smoothes" it out. As a second hypothesis, pore openings might limit halothane transfer into the granules or crystals and thereby limit adsorption rate. One would, therefore, approach equilibrium faster at a smaller *C*v (smaller *V*i), giving an apparently greater value for *P*. In this hypothesis, the apparent *P* would increase as equilibration time became longer and would become less dependent on *V*i. Because V^* is so small, it is less likely that very different adsorption processes operate at low and high halothane vapour phase concentrations. Finally, one might hypothesize that soda-lime granules are not homogenous in their water contents. In the manufacturing process, desiccated soda-lime granules are hydrated by exposure to water. Thus, a small and clinically insignificant quantity of dry granules might be included with those which have been hydrated. Even a small quantity of dry soda-lime would adsorb halothane and could produce the small but statistically significant V^* we have reported.

In the case of dry soda-lime, two parameters must be considered, the intercept V^* and the slope *g*. This suggests the existence of two separate processes. Since V^* represents such a significant uptake of halothane compared with the small *V*i values seen with fresh soda-lime, we are clearly dealing with a different phenomenon which is additive to the original solubility-like process. This process appears to be saturable and to operate at a low *C*v. It accounts for about 90% of the adsorption of halothane by dry soda-lime. Because it allows removal of such large amounts of halothane at low gas concentrations, it is the phenomenon that is responsible for the large uptake of halothane by canisters of dry soda-lime during clinical anaesthesia.

This saturable process may be analogous to adsorption by a molecular sieve. Molecular sieves are crystals which, to become activated, release certain components such as water of crystallization, so that passageways are opened in the crystalline structure (Griesmer, Jones and Lautensach, 1959). Suitable molecular species of a passing fluid can then move into the passageways and be captured within the crystal. As adsorbents, molecular sieves separate compounds on the basis of differences in molecular dimensions, polarity, or carbon-bond saturation. Only molecules small enough to enter the passageway can be adsorbed; polar molecules are adsorbed in preference to non-polar; unsaturated hydrocarbons are selected preferentially to more saturated hydrocarbons. Since halothane is a small, polar molecule, it seems a likely adsorbate. Since molecular sieves are commonly activated by heating to drive off water, it seemed reasonable that drying might activate soda-lime and allow it to adsorb passing halothane molecules.

A number of investigators have reported that small quantities of water, of the order of 1%, when presorbed on naturally occurring molecular sieves, can influence the subsequent adsorption of small polar and non-polar molecules (Barrer and Rees, 1954a, b; Ma et al., 1978). They noted that equilibrium adsorption results were highly dependent on temperature, amount and time of addition of presorbed water. They also observed that adsorption on the solid could continue slowly over a period of several days, causing the equilibria to "drift". They measured the rate of diffusion of the gaseous adsorbent as a function of presorbed water and concluded that changes in intracrystalline diffusion caused by blockage of pores by water molecules was the major factor in slowing the adsorptive processes. Thus these investigators report in an entirely different system a phenomenon similar to that which we have found with soda-lime. It may be that the presence of presorbed water on a porous crystalline solid, such as soda-lime, blocks passageways to a greatly increased adsorptive surface. However, the understanding of the exact nature of the halothane–soda-lime bond will require more direct measurements, such as from x-ray diffraction crystallography, differential thermal analysis and diffusion studies.

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MECHANISMES DE L'ABSORPTION DE L'HALOTHANE PAR LA CHAUX SODEE SECHE

RESUME

En utilisant de la chaux sodée fraiche (15% de son poids en eau), nous avons constaté que le coefficient de partition chaux sodée/air de l'halothane diminuait en fonction de la concentration d'halothane en phase vapeur, de 2,40 pour 0,3 volume pour 100 d'halothane jusqu'à 1,15 pour 2,6 volumes pour 100, tandis que l'adsorption suivait en général la loi de Henry. Cependant, de la chaux sodée hydratée pour rester à un poids constant et secondairement exposée à diverses concentrations d'halothane adsorbait environ 300 μ litre d'halothane liquide vaporisé pour 100 g avant que l'on puisse détecter une concentration mesurable d'halothane sous forme de vapeur. Si l'on ajoutait alors de l'halothane supplémentaire, il s'en suivait une augmentation linéaire de la concentraton de vapeur. Nous en concluons que la chaux sodée sèche peut absorber de grandes quantités d'halothane par un mécanisme comparable à un tamis moléculaire. Une fois que ces sites de "haute affinité" sont satisfaits, de l'halothane supplémentaire est adsorbé par un mécanisme suivant la loi de Henry.

MECANISMOS DE ABSORCION DE HALOTANO POR PARTE DE LA CALIZA SODICA

SUMARIO

Haciendo uso de caliza sódica (con un 15% de agua por peso), el coeficiente de repartición de aire y de carbonato para el halotano se encontró que disminuia cual una función de la concentración de halotano en su fase de vapor, descendiendo desde 2,40% a 0,3% de halotano por volµmen hasta 1,15% a 2,6%, auque la absorción siguió por lo general la ly de Henry. No obstante, la caliza sódica secada a un peso constante y posteriormente expuesta a diversas concentraciones de halotano, absorvió, aproximadamente, 320 µlitros de halotano líquido vaporizado por cada 100 g, antes de que se detectara en la fase gaseosa una concentración de halotano que pudiera medirse. El continuar añadiendo halotano orginó un incremento lineal de la concentración gaseosa. Concluimos que la caliza sódica seca puede absorber grandes cantidades de halotano mediante un mecanismo similar al de la criba por acción molecular. Una vez que estas zonas de "gran afinidad" están saturadas, se sige absorbiendo halotano mediante un mecanismo que sigue la ley de Henry.

Br. J. Anaesth. (1982), 54, 567

EFFECT OF NITROUS OXIDE ALONE OR ITS COMBINATION WITH FENTANYL ON SPINAL REFLEXES IN CATS

N. SUGAI, H. MARUYAMA AND K. GOTO

SUMMARY

The effects of nitrous oxide alone and combination of nitrous oxide and fentanyl on spinal reflexes were studied in cats with transected spinal cord at the thoracic level. Nitrous oxide 33, 50 and 75% in oxygen depressed the amplitude of monosynaptic reflexes in a dose-dependent manner, but exerted little effect on polysynaptic reflexes. The addition of fentanyl 2.5 μg kg^{-1} during the administration of 75% nitrous oxide in oxygen depressed monosynaptic reflexes further. These results suggest that nitrous oxide or its combination with fentanyl has a depressant action on the transmission of monosynaptic reflexes in the spinal cord, but nitrous oxide might exert less effect on the spinal interneurones which mediate polysynaptic reflexes.

Simultaneous administration of nitrous oxide and narcotics increases the rigidity of skeletal muscle in man (Hamilton and Cullen, 1953; Gergis, Hoyt and Sokoll, 1971; Sokoll, Hoyt and Gergis, 1972; Freund et al., 1973; Askgaard et al., 1977). The H-reflex, which is a monosynaptic reflex contributing to the skeletal muscle rigidity, is usually depressed by nitrous oxide in man (Gergis, Hoyt and Sokoll, 1971; Sokoll, Hoyt and Gergis, 1972; Freund et al., 1973).

However, there have been no detailed studies of the effect of nitrous oxide and fentanyl on the spinal reflex in an animal devoid of higher controls and the effect of these drugs on monosynaptic and polysynaptic reflexes is not known in detail. In the present study, the effect of nitrous oxide alone and its combination with fentanyl on the spinal reflex was studied in cats with the spinal cord transected at the thoracic level.

METHODS

Eight cats of both sexes, weights 1.8–4.0 kg (mean 3.1 ± 0.7 kg, SD) were studied. Tracheotomy was performed under ether anaesthesia and the femoral artery and cephalic vein cannulated. Arterial pressure was recorded throughout the experiment with a pressure transducer attached to the femoral arterial cannula. Arterial blood samples for gas analysis were drawn from this cannula. Fluid and drug administration was performed through the cephalic vein.

The cats were paralysed with gallamine 2 mg kg^{-1} and placed on a stereotactic apparatus. The lungs were ventilated with air using a Harvard ventilator. Arterial P_{O_2}, P_{CO_2} and pH were maintained within normal ranges. Sodium bicarbonate was given i.v. if necessary to correct metabolic acidosis.

Points of the cat which were in contact with the stereotactic apparatus were infiltrated with 1% lignocaine solution. Additional local application of lignocaine and i.v. administration of gallamine were performed when necessary throughout the course of the experiment. After local infiltration of the overlying skin and tissue with 1% lignocaine solution, laminectomy was performed at T10 and the spinal cord was transected at this level. Laminectomy was then performed at L6–S1.

The ventral and dorsal roots of L7 were dissected and cut. The exposed spinal cord was covered with a paraffin pool. Rectal temperature of the animal was maintained at 37 °C. The dorsal root of L7 was stimulated at 1 Hz with a square wave pulse of 200 μs duration. The intensity of the stimulus was set at 30% above the voltage at which the largest amplitude of the mono- and polysynaptic waves was obtained. This stimulation was considered as supramaximal.

Evoked potentials were recorded from the ventral root using a monopolar silver electrode. These spinal monosynaptic and polysynaptic reflexes were displayed on an oscilloscope and 32 waves were added by use of Adscope (Nihon-Kohden, Tokyo).

Control observations were made at least 3 h after cessation of inhalation anaesthesia using controlled

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ventilation with 100% oxygen. After 15 min, nitrous oxide in oxygen was administered at concentrations of 33, 50 and 75% for 10 min at each concentration. Nitrous oxide was then discontinued and 100% oxygen was given for 30 min. The gas mixture was readjusted to 75% nitrous oxide in oxygen for 10 min and fentanyl (Fentanest, Sankyo Co., Tokyo) 2.5 μg kg^{-1} was administered i.v.

Statistical analysis of the data was performed using Student's *t* test for paired data.

RESULTS

Figure 1 shows spinal reflexes observed in one cat during administration of 100% oxygen, and 33, 50 and 75% nitrous oxide in oxygen. Figure 2 shows reflexes of the same cat recorded during the recovery period with 100% oxygen administration, during administration of 75% nitrous oxide for the second time and after the addition of fentanyl 2.5 μg kg^{-1} i.v.

Nitrous oxide diminished the maximal amplitude of the monosynaptic reflex. Mean changes with SD compared with the control taken during oxygen administration were: −43.2 ± 20.7% with 33% nitrous oxide; −62.0 ± 14.8% with 50% nitrous oxide and −78.0 ± 11.2% with 75% nitrous oxide (fig. 3). These changes were all significant ($P < 0.001$). The amplitude of the monosynaptic reflex during air administration did not change significantly from that measured during administration of oxygen (−0.7 ± 18.0%).

Polysynaptic waves were affected less with administration of nitrous oxide. The first wave of the polysynaptic reflex was taken as representative of polysynaptic waves. These first waves showed no statistically significant changes (−15.0 ± 13.2% with air; −9.3 ± 31.4% with 33% nitrous oxide; −12.0 ± 49.1% with 50% nitrous oxide; −29.1 ± 55.1% with 75% nitrous oxide, all compared with the oxygen control) (fig. 3).

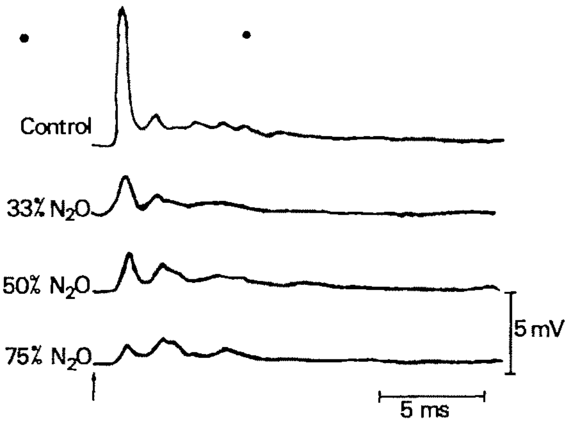

FIG. 1. Effect of nitrous oxide on spinal reflexes in cat with the spinal cord transected at T10. (Drawn from the original record.)

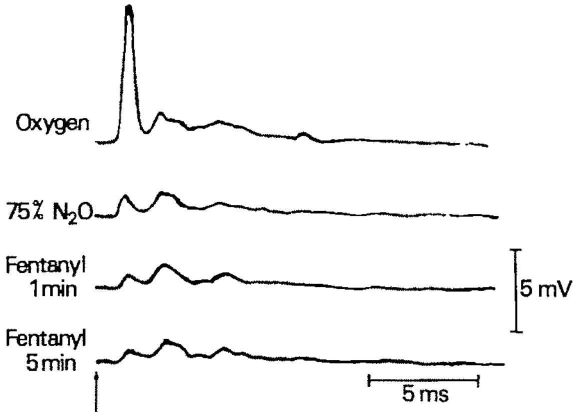

FIG. 2. Effect of 75% nitrous oxide and 75% nitrous oxide plus fentanyl 2.5 μg kg^{-1} on spinal reflexes. Recording continues from figure 1 on the same cat. (Drawn from the original record.)

After changing from nitrous oxide back to 100% oxygen, amplitudes of monosynaptic reflex waves recovered to −21.7 ± 27.8% of control. The second administration of 75% nitrous oxide in oxygen reduced the amplitude of the monosynaptic reflex to −72.4 ± 9.9% compared with the value taken during the second administration of 100% oxygen ($P < 0.01$).

When fentanyl 2.5 μg kg^{-1} was given the amplitude of the monosynaptic reflex was depressed (−26.7 ± 12.0% 1 min after fentanyl; −29.6 ± 16.8% 3 min after fentanyl; −36.5 ± 13.9% 5 min after fentanyl; all compared with the value taken during the second administration of 75% nitrous oxide). These changes are all statistically significant ($P < 0.01$, $P < 0.05$ and $P < 0.01$ respectively). Polysynaptic reflexes after fentanyl administration became fused in some cases and it was difficult to identify the first polysynaptic wave.

DISCUSSION

In the present study, nitrous oxide decreased in a dose-dependent manner the amplitude of spinal monosynaptic reflexes in cats with transected spinal cord at the thoracic level. Amplitudes of polysynaptic reflexes were affected little with nitrous oxide.

It has been demonstrated that increased rigidity of skeletal muscle occurs when nitrous oxide, a narcotic or their combination is given to man

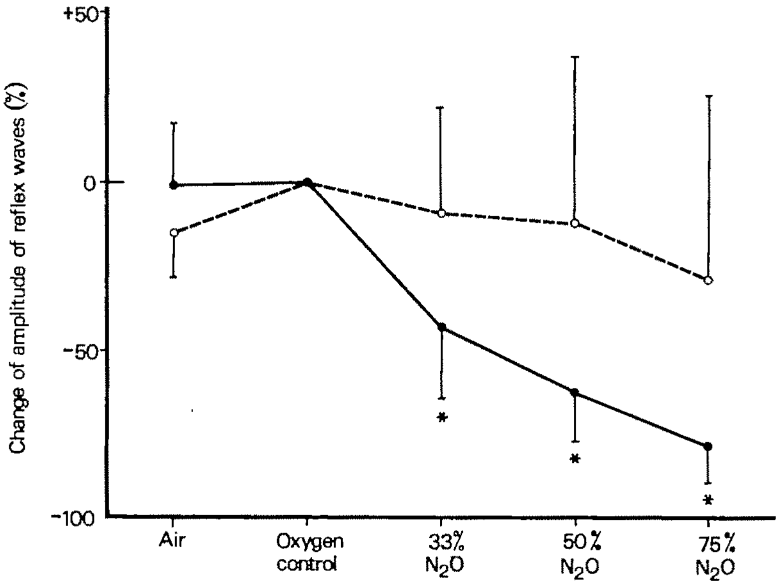

FIG. 3. Percent changes (means ± SD) from the control taken during administration of 100% oxygen, of the amplitude of monosynaptic reflexes (●——●) and the amplitude of the first wave of polysynaptic reflexes (○—○). Asterisks show significant changes ($P<0.001$).

(Hamilton and Cullen, 1953; Gergis, Hoyt and Sokoll, 1971; Sokoll, Hoyt and Gergis, 1972; Freund et al., 1973; Askgaard et al., 1977). Gergis, Hoyt and Sokoll (1971) showed that H-reflex was depressed by nitrous oxide and Innovar in man and Sokoll, Hoyt and Gergis (1972) later demonstrated that fentanyl, morphine and meperidine increased the amplitude of H-reflex in man but nitrous oxide reduced the amplitude. Ngai, Hanks and Farhie (1965) using cats showed that 80% nitrous oxide depressed the amplitude of crossed-extensor reflexes. Similarly in cats, de Jong and others (1968) demonstrated that 77% nitrous oxide depressed the monosynaptic reflex and also had synergistic effect with halothane and ether in depressing monosynaptic reflexes.

Systematic studies, however, on the effect of nitrous oxide and fentanyl on the spinal reflexes in animals devoid of higher nervous control has not been undertaken.

This study in cats with transected spinal cord at the thoracic level demonstrated that the effect of nitrous oxide on the spinal monosynaptic reflex was depressive and the depression was dose-dependent. These findings in transected cats suggest that nitrous oxide depresses directly the mechanism involved in the genesis of the spinal monosynaptic reflex.

It seems that the polysynaptic reflex is resistant to the depressive effect of nitrous oxide compared with the monosynaptic reflex. According to Bárány's theoretical analysis (Bárány, 1947), a multisynaptic chain in the central nervous system is always more vulnerable to the effect of anaesthetics than an oligosynaptic pathway, other factors being equal. Experimental evidence, however, showed that the number involved is not the only determinant of the effect of anaesthesic agents on the synapses in the central nervous system (Megirian, Vasey and Posternak, 1958; Somjen, 1967).

For instance, in Megirian's experiments, ethanol and n-pentanol depressed the polysynaptic pathway to a greater extent than the monosynaptic pathway in the spinal cord. Ether and chloroform exerted no such selective action. According to Esplin (1959), carbon dioxide depresses the monosynaptic reflex but it has less effect on polysynaptic pathways. In this respect, the action of nitrous oxide demonstrated in the present study could be similar to that of carbon dioxide.

Sokoll, Hoyt and Gergis (1972) reported that fentanyl increased the amplitude of the human H-reflex. In Rudakov's experiment in cats (1971), decreased amplitude of the polysynaptic response was observed with administration of fentanyl 0.25 mg kg^{-1}. Monosynaptic reflex was unchanged even with larger doses of fentanyl. In the present study, fentanyl potentiated the depression of monosynaptic reflex caused by 75% nitrous oxide.

The results of the present study suggest that nitrous oxide or its combination with fentanyl depresses the spinal monosynaptic pathway, but spinal interneurones which transmit polysynaptic reflexes are affected less by nitrous oxide alone. This selective action might have some relation to the muscle rigidity observed with nitrous oxide and narcotics.

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EFFETS DU PROTOXYDE D'AZOTE SEUL OU ASSOCIE AU FENTANYL SUR LES REFLEXES MEDULLAIRES DU CHAT

RESUME

Les effets du protoxyde d'azote seul ou associé au fentanyl sur les réflexes médullaires ont été étudiés sur des chats ayant une section transversale de la moëlle au niveau thoracique. Le protoxyde d'azote (33,5% et 75% dans l'oxygène) diminue l'amplitude des réflexes monosynaptiques de façon dose-dépendante, mais a peu d'effets sur les réflexes polysynaptiques. L'adjonction de fentanyl 2,5 $\mu g\,kg^{-1}$, pendant l'administration de protoxyde d'azote à 75% dans l'oxygène déprime encore davantage les réflexes monosynaptiques. Ces résultats suggèrent que le protoxyde d'azote seul ou en association avec le fentanyl a une action dépressive sur la transmission des réflexes monosynaptiques dans la moëlle épinière, mais que le protoxyde d'azote pourrait exercer un effet moindre sur les interneurones médullaires par lesquels transitent les réflexes polysynaptiques.

EFECTO DEL OXIDO NITROSO, SOLO O EN COMBINACION CON FENTANILO, EN LOS REFLEJOS DE LA ESPINA DORSAL DE LOS GATOS

SUMARIO

Se estudiaron los efectos del óxido nitroso, solo o en combinación con fentanilo, en los reflejos de la espina dorsal de los gatos con espina cruzada al nivel toráctico. Concentraciones de 33,5% y de 75% de óxido nitroso en oxígeno redujeron la amplitud de los reflejos monosinápticos en función de la dosis, pero ejercieron poco efecto sobre los reflejos polisinápticos. La incorporación de 2,5 $\mu g\,kg^{-1}$ de fentanilo durante la administración de óxido nitroso en óxigeno (75%) deprimió más aún las reflejos monosinopticos. Estos resultados sugieren que el óxido nitroso, solo o en combinación con fentanilo, posee una influencia reductora sobre la transmisión de los reflejos monosinápticos en la espina dorsal, pero puede que su influencia sea menor en las interneuronas de la espina dorsal relativas a los reflejos polisinápticos.

Br. J. Anaesth. (1982), 54, 571

CORRESPONDENCE

METHAEMOGLOBIN FORMATION AFTER NITROGLYCERIN INFUSION

Sir,—Treatment with organic nitrates has been associated with the formation of methaemoglobin (Fibuch, Cecil and Reed, 1979), and since nitroglycerin (NTG) infusion is being widely used as a vasodilator (Kaplan, Finlayson and Woodward, 1980) this potential risk may have to be considered. The following observation suggests that methaemoglobin formation may be without significance during NTG infusion.

A 44-yr-old woman who had been using ergotamine for many years because of migraine was admitted with overt ergotism: examination revealed the absence of peripheral pulses and decreased peripheral systolic arterial pressures. While the systemic arterial pressure, central venous pressure, heart rate and peripheral systolic pressures (determined by strain gauge plethysmography) were monitored the patient received an infusion of NTG in incremental doses (Husum, Metz and Rasmussen, 1979; Tfelt-Hansen et al., 1982). Vasodilatation did not appear until the infusion rate was as much as $8\,\mu g\,kg^{-1}\,min^{-1}$. After 24 h of treatment with NTG $8\,\mu g\,kg^{-1}\,min^{-1}$ (the total amount of NTG being approximately 690 mg), spectrophotometric analysis of the patient's haemoglobin revealed a methaemoglobin fraction of 0.037. The patient was discharged from hospital without any symptoms of ergotism.

Usually the infusion rate of NTG is 0.5–$3.0\,\mu g\,kg^{-1}\,min^{-1}$ (Kaplan, Finlayson and Woodward, 1980). Because NTG $8\,\mu g\,kg^{-1}\,min^{-1}$ in our patient produced only small amounts of methaemoglobin, we conclude that, when used in standard doses of 0.5–$3.0\,\mu g\,kg^{-1}\,min^{-1}$, NTG will not normally induce methaemoglobin in clinically significant amounts.

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ALGEBRA AND THE CIRCLE SYSTEM

Sir,—The circle system continues to be an irresistible attraction, on both sides of the Atlantic, to virtuosos of algebra and respiratory physiology. When the symbols of both are combined, few readers will make the effort to follow calculations such as those of Professor Conway (1981). Now that it is possible to measure accurately the oxygen, enflurane or halothane concentration and to deduce the nitrogen concentration in any part of a circle system, can we not look forward to an end to the algebra (Hamilton, 1980)?

Professor Conway's paper repeats the unnecessary advice that high gas flows should be used for 20 min before the system is closed. The nitrogen concentration in the FRC and the circuit can be reduced to less than 4% in less than 3 min (Linn, Mostert and Benson, 1980) and it is then feasible to close the circuit provided that F_{IO_2} is held constant at 0.3. The 0.5 litre or so of tissue nitrogen which will accumulate in the next 30 min can be purged by a very brief period of high flow if this is desirable.

Provided the circuit is closed, the buffering effects of the system can be fully relied upon, in spite of Professor Conway's statement to the contrary. It is because of this that oxygen failure, for example, will take several minutes to reduce the inspired oxygen concentration by 10% and what other system can match this? It is possible to use a closed system after 3 min of high flows and to guarantee that the F_{IO_2} will remain greater than 0.3, nitrogen will never exceed 8% and the nitrous oxide concentration will be in the range 0.5–0.6 MAC without measuring any gas concentration in the circuit itself. I do not advocate this except to demonstrate that the system is inherently predictable and safe when used with ordinary flowmeters.

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Sir,—Learned journals commonly publish a variety of papers, reflecting the varied and catholic interests of both their contributors and readers. Of necessity not all the papers that such journals contain will appeal equally to all readers. Dr Horsey casts scorn on the use in my paper (Conway, 1981) of a combination of respiratory physiology and algebra. What other approach would he expect to find in a paper which in both its title and summary obviously sets out to attempt a theoretical explanation of circle system behaviour? He would have been fully justified in deriding my contribution had it merely consisted of the assertions made in its discussion section without giving the necessary theoretical basis for making these assertions, and would command serious respect if he could show that this theory was in any way in error.

Like Dr Horsey, I look forward to an "end to the algebra", especially if this implies the use of low-flow systems based on sound and safe tenets rather than the individualistic, intuitive or even mystical approaches which abound in the practice. One must, however, totally reject the application to any branch of medicine of the approach he advocates—that if we can measure the results of what we do, it is unnecessary to understand the processes we are using. Empiricism has its place, but is no substitute for proper understanding.

The final sentence of my paper consisted of a strong recommendation to monitor gas concentrations when using low flow systems. Like Dr Horsey, we have the equipment necessary for such measurements. Many users of circle systems do not have such monitoring equipment readily to hand. If they follow Dr Horsey's advice, they may easily put their patients in hazard.

If nitrous oxide is to be used in a circle system, then both theory and published results dictate the use of an initial period with high fresh gas flows. Barton and Nunn (1975) found nitrogen concentrations much greater than those claimed by Dr Horsey after 10 min of denitrogenation. If inspired oxygen concentration is monitored and held constant then hypoxia can be avoided, but nitrous oxide concentration will be reduced by nitrogen dilution. This is an inefficient approach to anaesthetic practice. By contrast, if no nitrous oxide is used there may be advantages in avoiding any period of denitrogenation. To do this would result in nitrogen concentration in the system increasing to about 50%, and this would prevent unnecessarily high oxygen concentrations being delivered to the patient.

There is little place in serious medical literature for the anecdotal statement. Dr Horsey ends his letter with an unsubstantiated and dangerous claim on the safety of closed systems even without monitoring. He does not tell us how he produces his guaranteed safe conditions. By the same token and with suitable and apparently safe choices of fresh gas flow and composition, one can guarantee to produce in closed systems oxygen concentrations which either approach zero or increase above 90%. I would not recommend anyone to test either this claim or that of Dr Horsey on their patients.

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LEAK TESTS

Sir,—Several issues are raised by the account of a torn flow meter seal that produced hypoxic mixtures (Powell, 1981). Modern anaesthetic machines and their breathing systems may leak between (1) the cylinder or pipeline attachment and the flowmeter needle valve; (2) the needle valve and the back check/pressure relief valve; (3) the latter valve and the patient.

Commonly, the anaesthetic machine is "tested" with the Magill attachment in position. The Heidbrink valve is screwed down, the patient end of the attachment is occluded, and the bag is filled and then squeezed to detect a major leak that would prevent inflation of the patient's lungs. This test will detect a bad connection between the Magill attachment and the anaesthetic machine, a torn bag or a faulty Heidbrink valve. However, it is important to realize that this crude test indicates nothing about the safety of the machine before the back check valve. An apparently more sensitive version of this test uses flows of oxygen and nitrous oxide 500 ml min^{-1}. If the flowmeter bobbins dip when the bag is squeezed one might suppose that there can be no leak approaching 1 litre min^{-1}. Unfortunately, when we simulated a leaking rotameter we discovered that this test does not detect leaks of this order.

A dynamic pressure test (Page, 1977) is required to detect leaks between the needle valve and the back check valve. The outlet of the anaesthetic machine is connected to a pressure gauge, and the oxygen needle valve is slowly opened and adjusted to maintain a steady pressure of 16 kPa. The flow on the flowmeter is an indication of the leakage and more than 200–300 ml min^{-1} is unacceptable. An adaptor can easily be made to connect the anaesthetic machine outlet to a manometer so that this can become part of the daily check. A static test to see if pressure can be maintained will not detect leaks occurring before the back check valve and so will miss a leaking rotameter (Powell, 1981).

Alternatively, if a ventilator powered from the fresh gas outlet of the anaesthetic machine will cycle with an oxygen flow of only 500 ml min^{-1}, any leak in either the anaesthetic machine or ventilator must be less than this. For example, if a Manley ventilator is used, the weight is placed to the far right-hand side of the arm and with the switch in the "automatic" position a high flow of oxygen is provided until the arm rises; the flow is reduced to 500 ml min^{-1} and the arm should continue to rise very slowly. (Note that this does not check for leaks in tubes to and from the patient or in the expiratory valve.)

A cracked flowmeter may produce a hypoxic mixture and a manifold has been designed which contains an inner tube to release oxygen at the right-hand side of the bank of rotameter tubes. However, this ingenious arrangement would not protect against the effect of a torn oxygen flowmeter seal or a cracked oxygen flowmeter; nor does it prevent a cracked nitrous oxide flowmeter leaking thus risking awareness during anaesthesia. Consequently a leak test is still essential.

We simulated a leak by opening the cyclopropane needle valve (since neither reducing nor back check valves are present for this gas) and allowing gas to escape backwards through the empty yoke. This serves as a reminder that, when the machine is checked before use, unwanted flowmeters should be turned off and, ideally, empty yokes should be blanked lest a hypoxic mixture be created through this route.

Finally, as leak checks may require expiratory valves to be closed, it is important to remember to release them before use. Failure to do this is a common cause of anaesthetic mishap (Newton and Adams, 1978; Craig and Wilson, 1981).

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WAKEFULNESS AND GENERAL ANAESTHESIA

Sir,—The suggestion that the isolated forearm technique (Tunstall, 1977) is impracticable during general surgical procedures and less sensitive than clinical signs in the detection of light planes of anaesthesia (Breckenridge and Aitkenhead, 1981) deserves further comment.

There are several areas of doubt in the technique described by Breckenridge and Aitkenhead. First the minor problem of semantics: any procedure relying on a patient's memory after surgery will detect awareness, but by definition will not detect wakefulness (Tunstall, 1977). The second more serious problem is the complexity of their command. We know very little of mental processes under light anaesthesia and it is quite possible that the original instructions had been forgotten by the time the electronic signal was presented. Also it is accepted widely that patients will be aroused by a meaningful stimulus such as their name more frequently than by a non-meaningful stimulus. Thus it is equally possible that the electronic stimulus was not heard. A simple command to squeeze with a particular hand is sufficient, although admittedly it lacks the stimulus–response relationship on the recording paper. My third point is to draw attention to the contradictions between their conclusions and findings. They found surgery impossible because of purposeful movement of the isolated arm, yet concluded that the isolated arm provided a less sensitive index than clinical signs. Presumably the clinical signs suggested adequate anaesthesia before surgery commenced. However, because the arm moved purposefully, surgery stopped. Surely this is a valuable sign of inadequate anaesthesia, and to release the tourniquet (thus paralysing the arm) to allow surgery to procede without deepening anaesthesia is a questionable decision. The subsequent continuous surgical stimulation could cause sufficient arousal for the patient to become wakeful, but there may be no means of detecting this. After four years' experience of the technique in general surgery I have not yet resorted to deflating the tourniquet for this reason since a small dose of induction agent combined with an increased halothane concentration or increment of analgesic will suffice. Unfortunately a further dose of relaxant seems to be the treatment of choice for patients who move during surgery. Even when it is demonstrated that the patient can obey commands many trainees would still administer a muscle relaxant "to stop the patient moving". This response is evidently something they have been taught since they show great reluctance to deepen anaesthesia.

When tracheal intubation is performed with the aid of suxamethonium an assessment of consciousness should be made before injecting the non-depolarizing agent, especially if the isolated arm technique is not to be used. I could not agree more with Wilson (1981) when he encourages readers to give the technique a fair trial, since there is an abundance of evidence that clinical signs of anaesthesia cannot be relied upon to detect awareness or wakefulness.

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MAGILL INTUBATING FORCEPS

Sir,—About a year ago I had a pair of Magill intubating forceps made with blades 5 cm longer than the standard adult pattern. When used with the large Magill laryngoscope blade they can reach into the upper end of the oesophagus, and have solved the problem of introducing a nasogastric tube, oesophageal stethoscope, or the tail of a Celestin tube.

We were so pleased with this modification that we asked for six more pairs to be ordered. Our excellent hospital Supplies Officer carefully provided Area Staff with all the necessary information, specifying particularly the original manufacturer, who understood exactly what was required. The Area Supplies Department, however, obtained a cheaper quotation elsewhere.

Magill forceps with elongated blades can be obtained from Seward Surgical, UAC House, Blackfriars Road, London SE1 9UG; a limited number of Magill forceps with elongated handles are available from the Enfield and Haringey Area Supplies Department.

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MORPHINE AND THE EXTRADURAL SPACE

Sir,—Information on the adverse effects of morphine on the extradural space is still sparse: we treated a 59-yr-old man with intractable tenesmus for 6 months using extradural morphine 4–6 mg two or three times daily. The patient had had radiotherapy, and had undergone cystectomy with utero–ileo–cutaneostomy.

The autopsy showed tumour masses and fibrosis in the pelvis and widespread metastases.

Slight oedema and brown discoloration of the dura mater and the extradural space were seen at the location of the catheter tip, but there were no adhesions nor signs of infection.

Microscopy showed a normal dura mater. At the tip of the catheter, the extradural space consisted of vascular and hyperaemic connective tissue with a few lipophages, clefts caused by cholesterol crystals, multinuclear giant cells of foreign body type, scattered macrophages containing haemosiderin and small accumulations of lymphocytes and plasma cells.

Histological examination of various levels of the injection track showed no oedema, haemorrhage or granulomatous reaction. Bacteria and fungi were not seen. It was concluded that these were slight reactive changes, probably resulting from haemorrhage.

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RESISTANCE TO PANCURONIUM AND HAEMOCONCENTRATION

Sir,—Schuh (1981) has shown that the potency of neuromuscular blocking drugs is increased following normovolaemic haemodilution. This has been attributed to a decrease in blood viscosity and peripheral resistance which increases the regional blood flow, particularly to skeletal muscle, resulting in a more rapid initial uptake of the neuromuscular blocking drugs. Also, a decrease in serum protein concentration may be followed by a decreased protein binding capacity leading to a higher concentration of unbound free and pharmacologically active neuromuscular blocking drugs.

In contrast, haemoconcentration may produce resistance to neuromuscular blocking drugs as observed in two children with congenital cyanotic heart disease (Fallot tetralogy; transposition of great vessels with VSD). In both children before operation, Pa_{O_2} was 30 mmHg, Hct was 70 and plasma protein concentrations were within the normal range. Anaesthesia was induced with ketamine 2 mg kg^{-1}, followed by pancuronium. Optimal relaxation necessary for tracheal intubation was only achieved with pancuronium 0.35 mg kg^{-1} in the patient with Fallot tetralogy and 0.40 mg kg^{-1} in the patient with transposition. These doses are about three or four times the usual doses.

Such resistance to pancuronium cannot be explained by the right-to-left intracardiac shunt, which can slow the rate of uptake of inhalation anaesthetics (Eger, 1974). Conversely, drugs administered i.v. will reach the systemic circulation rapidly via the shunt without traversing the lung. The unexpected resistance to i.v. pancuronium may be attributed to the excessive haemoconcentration associated with the cyanotic heart diseases. Haemoconcentration will produce a mirror-image effect of haemodilution. It increases the viscosity and peripheral resistance, resulting in a decrease of regional blood flow to muscles. It is also possible that pancuronium and perhaps other neuromuscular blocking drugs are directly bound to the structural stroma that envelops the RBCs, or to the anionic sites of the stroma-bound acetylcholinesterase enzyme. Increased binding to the high RBC mass can lead to a lower concentration of the unbound free drug. It may be concluded that smaller doses of neuromuscular blocking drugs are required in patients having normovolaemic haemodilution, while larger doses are needed with haemoconcentration.

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POSTERIOR FOSSA SURGERY

Sir,—Dr Walters and Mr Torrens (1982) have drawn attention once again to the well documented hazards of the sitting position and state that the prone or semi-prone positions provide satisfactory operating conditions for infratentorial and cervical surgery. However, in support of their case for abandoning the sitting position they have quoted inaccurately from reference sources to give a misleading impression concerning the frequency and mortality of venous air embolism. Ericsson, Gottlieb and Sweet (1964) considered reports of 93 patients who presented with profound cardiovascular collapse or a precordial mill-wheel murmur, or both; 40 of these patients received no treatment at all and the mortality was 73%. In their own series of seven patients, five received closed-chest cardiac massage and resuscitation was successful; the mortality was 28%. These authors emphasized the importance of early detection at a time before the routine use of intra-arterial pressure measurement or the detection of small volumes of air by Doppler ultrasound or end-tidal carbon dioxide monitoring. Michenfelder, Miller and Gronert (1972), using a Doppler device, detected emboli in 20 of 69 patients in only one of whom were there clinical signs. In two further patients clinical signs of embolism developed without positive Doppler activation; the overall frequency was therefore 32% and not 93% as suggested by Dr Walters and Mr Torrens. There were no deaths in this series.

In my own practice a major air embolism has occurred on nine occasions during a period extending for 24 years. There was one fatality which occurred at a time when sophisticated detection techniques were not available.

The statement that the sitting position allows the surgeon to orientate himself better is an expression of opinion that more than one surgeon has made to me. Although amusing, the comments on the supine and lithotomy positions, which evoke visions of hitherto unreported surgical contortions, are irrelevant in the present context.

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Br. J. Anaesth. (1982), **54**, 575

BOOK REVIEWS

Fibrinolysis. By Neville Marsh. Published (1981) by John Wiley & Sons, Chichester, New York, Brisbane and Toronto. Pp. 254; illustrated; indexed. Price £16.50.

This book summarizes fibrinolysis and explores some of the enigmas associated with this subject. Following an introductory chapter dealing with the history of the subject and describing in broad terms the fibrinolytic system, there follows a detailed discussion of the mechanisms of activation of plasminogen, the formation of fibrin, and its subsequent lysis. The effects on fibrinolysis, of physiological and environmental factors such as exercise, diet and stress, are considered. A chapter on the relationships between disease and fibrinolysis includes discussion of disseminated intravascular coagulation, hepatic and renal disease, obstetric problems and malignancy. There is a detailed description of biological and pharmacological agents which inhibit or enhance fibrinolysis, and their mechanisms of action.

The complexity of the fibrinolytic system becomes evident to the reader at an early stage, and it is reassuring to find towards the end of the book a chapter providing a clear exposition of the normal function of fibrinolysis and its control mechanisms. Included in the text are the author's own thoughts concerning the present state of knowledge of the subject, and possible avenues for future research. The book ends with an extensive appendix dealing with technical aspects of measurement of fibrinolysis and fibrinolytic components.

This book is comprehensive and clearly written. More than a quarter consists of references, many of which are duplicated, and there is a thorough index.

Few anaesthetists will need to acquire the depth of knowledge of fibrinolysis afforded by reading this book in its entirety. However, the sections on clinical and therapeutic aspects would be of value to a great many, particularly those involved with intensive therapy or with an interest in vascular diseases.

A. R. Aitkenhead

Paediatric Anaesthesia. Trends in Current Practice. Edited by G. Jackson Rees and T. Cecil Gray. Published by Butterworths, London. Pp. 194; illustrated; indexed. Price £15.

The subtitle of this book suggests that it will contain discussion of the latest methods and innovations in the field of paediatric anaesthesia. The editors in their preface make it abundantly clear that this is not their intention. They hope to have produced a guide for the anaesthetist who has occasionally to deal with small children. This aim is excellently achieved by several of the contributors. The chapters by Inkster on apparatus, Stewart and Nisbet on anaesthetic and narcotic agents in the child, Kay on fluid therapy and especially the two chapters by Elena Vivori describing the "Liverpool" approach to paediatric anaesthesia, all give valuable and positive advice to the occasional paediatric anaesthetist. Other contributors have wandered far from the editors' brief. Bush's chapter on neuromuscular blocking agents is in the main a scholarly review of the sensitivity of the neonate to relaxants, with little advice on which drug to use and how to use it. Hatch, in discussing respiratory function assessment in children, describes briefly the practical clinical methods of respiratory measurement and devotes most of his chapter to methods of measurement more suitable to a research laboratory or a sophisticatedly equipped neonatal intensive care unit. Abbott gives an excellent and comprehensive account of the problems of anaesthesia for cardiac surgery in infants, but his contribution must surely be of little value to a reader likely to profit from the rest of the book.

The mixed nature of this book may represent a flaw in the editors' reasons for not wishing to write a textbook of paediatric anaesthesia. The occasional paediatric anaesthetist, hastening to be enlightened before tackling an unfamiliar problem, requires a much wider range of didactic advice than that available here. He might have been better served if the several contributors, who represent an elite amongst practising paediatric anaesthetists, had described their own methods of dealing with the specific problems of anaesthetizing small children. Such a textbook would have been a valuable contribution to the literature and would serve a far wider audience than this book ever can.

C. M. Conway

Handbook of Percutaneous Central Venous Catheterisation. By M. Rosen, I. P. Latto and W. S. Ng. Published (1981) by W. B. Saunders Co. Ltd. Pp. 134; illustrated; indexed. Price £6.95.

The purpose of this book, according to the authors' preface, is to bring together in one volume a large selection of routes and techniques for catheterization of the central veins. The introductory chapters outline the indications and contraindications of the routes available, describe venepuncture technique, and summarize the types of central venous catheterization equipment available. A chapter is devoted to practical aspects of technique, such as prevention of air embolism, catheter positioning and fixation, and prevention of infection and thrombus formation. This chapter also contains a detailed description of the insertion of a flow-directed pulmonary artery catheter. Readers who follow the recommendation of the authors to introduce a 7-French gauge pulmonary artery catheter through a 12-gauge cannula are in for an unpleasant surprise: the importance of checking that all the equipment is of a suitable size before starting the procedure does not receive a mention.

Seventy per cent of the text is devoted to details of the insertion of catheters at various sites. In separate chapters, cannulation of arm, subclavian, internal jugular, external jugular and femoral veins are described in a uniform format. The anatomy is outlined, the alternative approaches summarized, and the preferred method of the authors stated. Well illustrated, step-by-step instructions are given for each of the techniques chosen, and a table provided summarizing the reported success rate and complications. These chapters become fairly repetitive: 11 slightly different approaches to the internal jugular vein are described in detail. However, the stated purpose of the book is not to provide instruction for the novice, but to describe for the experienced clinician alternative approaches and their relative advantages if his normal method is inappropriate or unsuccessful. In this regard, the book succeeds. The literature search has been extensive, and the lists of complications and success rates appear to be comprehensive. The index is excellent. There are very few printing errors.

For the trainee, the book is rather too comprehensive and might lead to confusion. While the line drawings are adequate for the descriptions of variations of technique, the book lacks detailed anatomical artwork. However, the authors stress that inexperienced clinicians should not attempt central venous catheterization, particularly using neck veins, without supervision.

This is an excellent book, which will be an invaluable aid to all doctors who catheterize central veins regularly; indeed, it should be essential reading.

A. R. Aitkenhead

Handbook of Intensive Care. By R. S. Atkinson, J. J. Hamblin and J. E. C. Wright. Published (1981) by Chapman & Hall Ltd, London. Pp. 386; illustrated; indexed. Price £16.50.

This book attempts to set down the principles of intensive care as they concern the typical district general hospital. The authors state that they have tried to maintain simplicity and to give practical advice and have aimed the book at the junior doctor who takes his turn working in the intensive care unit.

There is some good basic information on underlying medical conditions, and in parts the book is particularly good on practical advice, for example the section on mechanical ventilation, in which a useful section is found on what to do should efficient ventilation fail. However, simplicity is overdone at times and the standard is patchy throughout.

The information contained on basic monitoring techniques is insufficient as is demonstrated by the sections on central venous pressure measurement. This topic is scattered throughout the book and the somewhat inadequate index did not help in chasing this very important subject. There is no mention of the normal value, and this occurs frequently with other physiological variables. Blood gases are quoted in mm Hg, or kPa without explanation or consistency. How can the junior doctor monitor and treat with such a lack of pathophysiological information? Conflicting information exists too, as is exemplified by the two different statements on direct arterial monitoring: one favouring the femoral route in preference to the radial artery and the other where the former is not recommended.

This book was sadly disappointing in many areas, but overall contains information which may justify its inclusion on the bookshelves of some intensive care units. The excellent reference lists at the end of each chapter should promote further interest in the topics covered.

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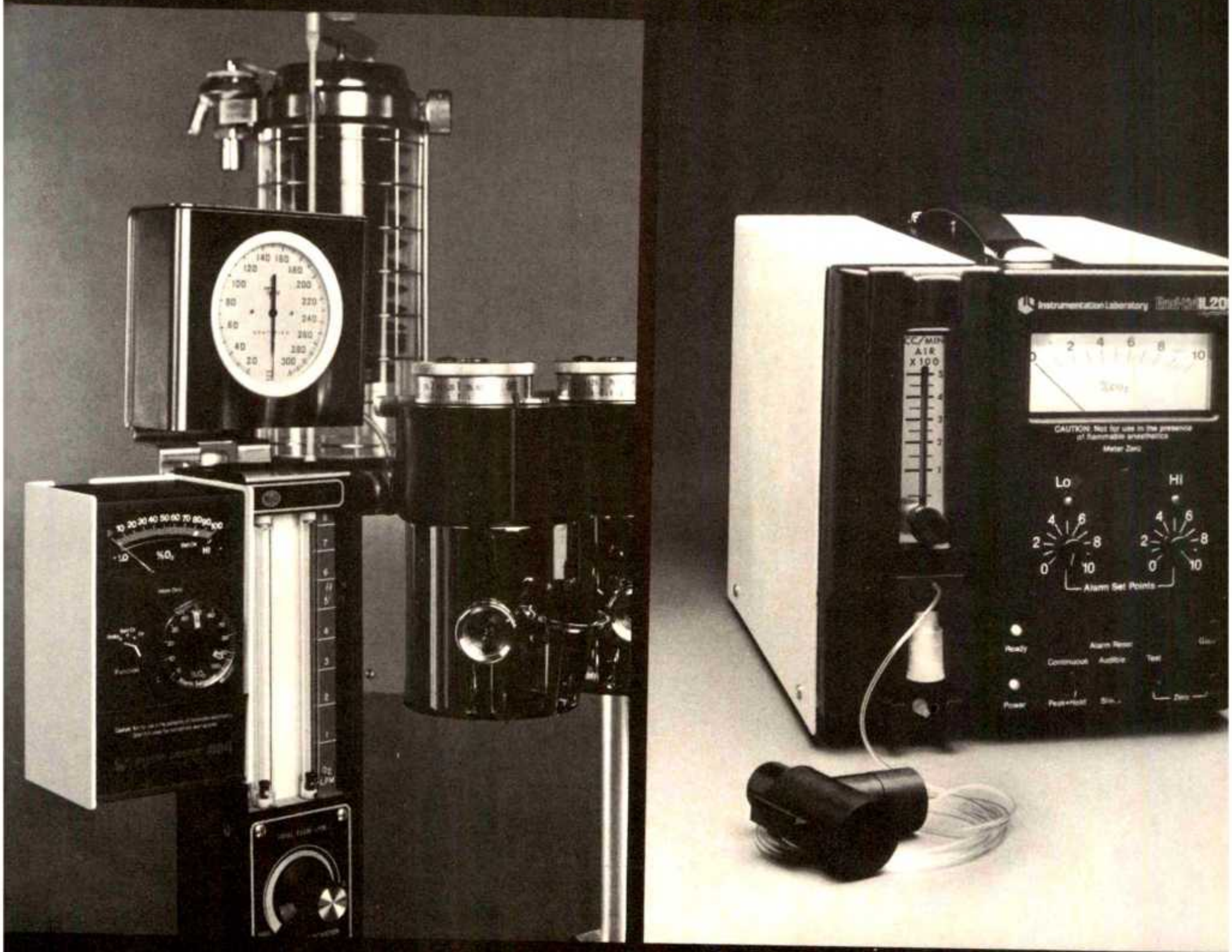

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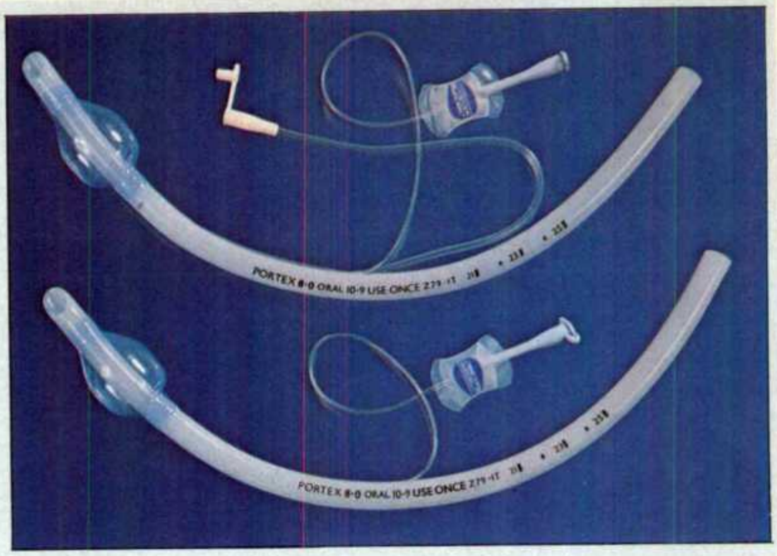

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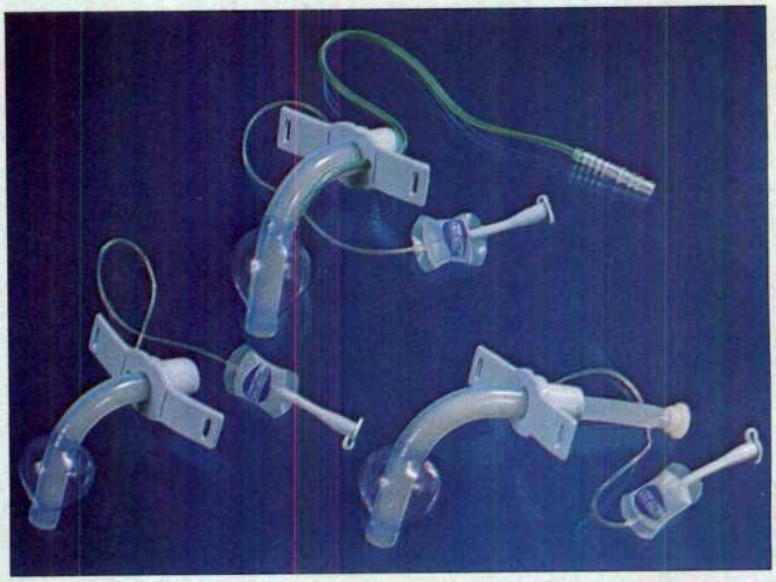

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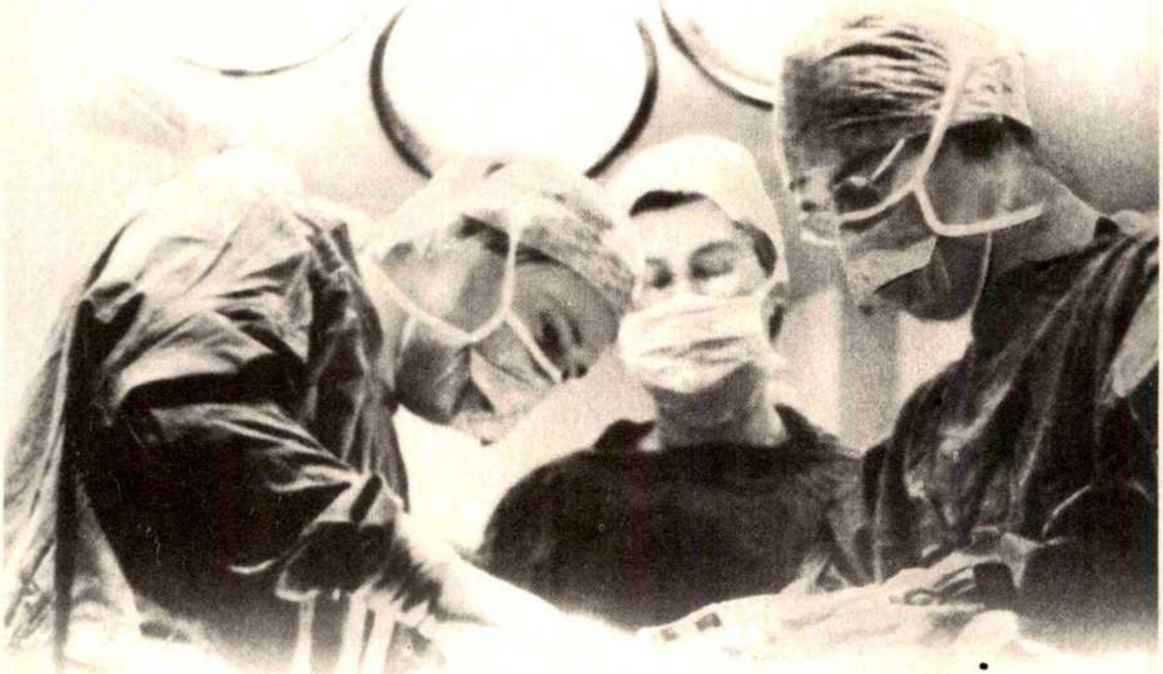

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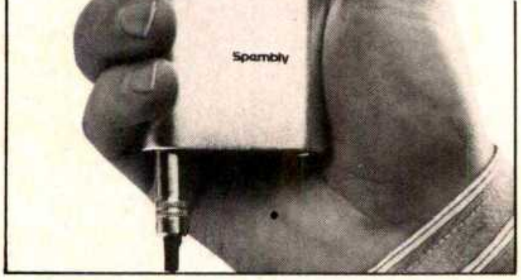

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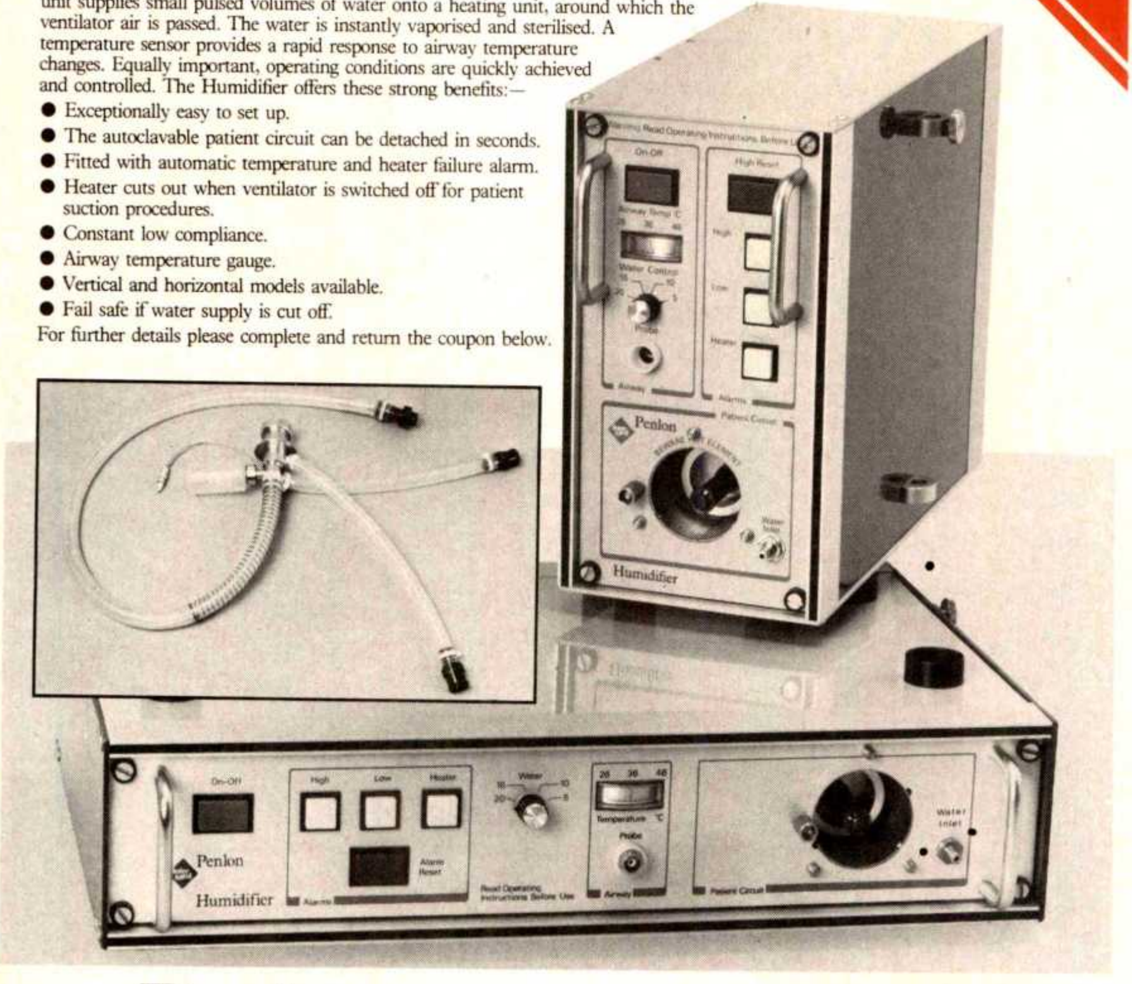

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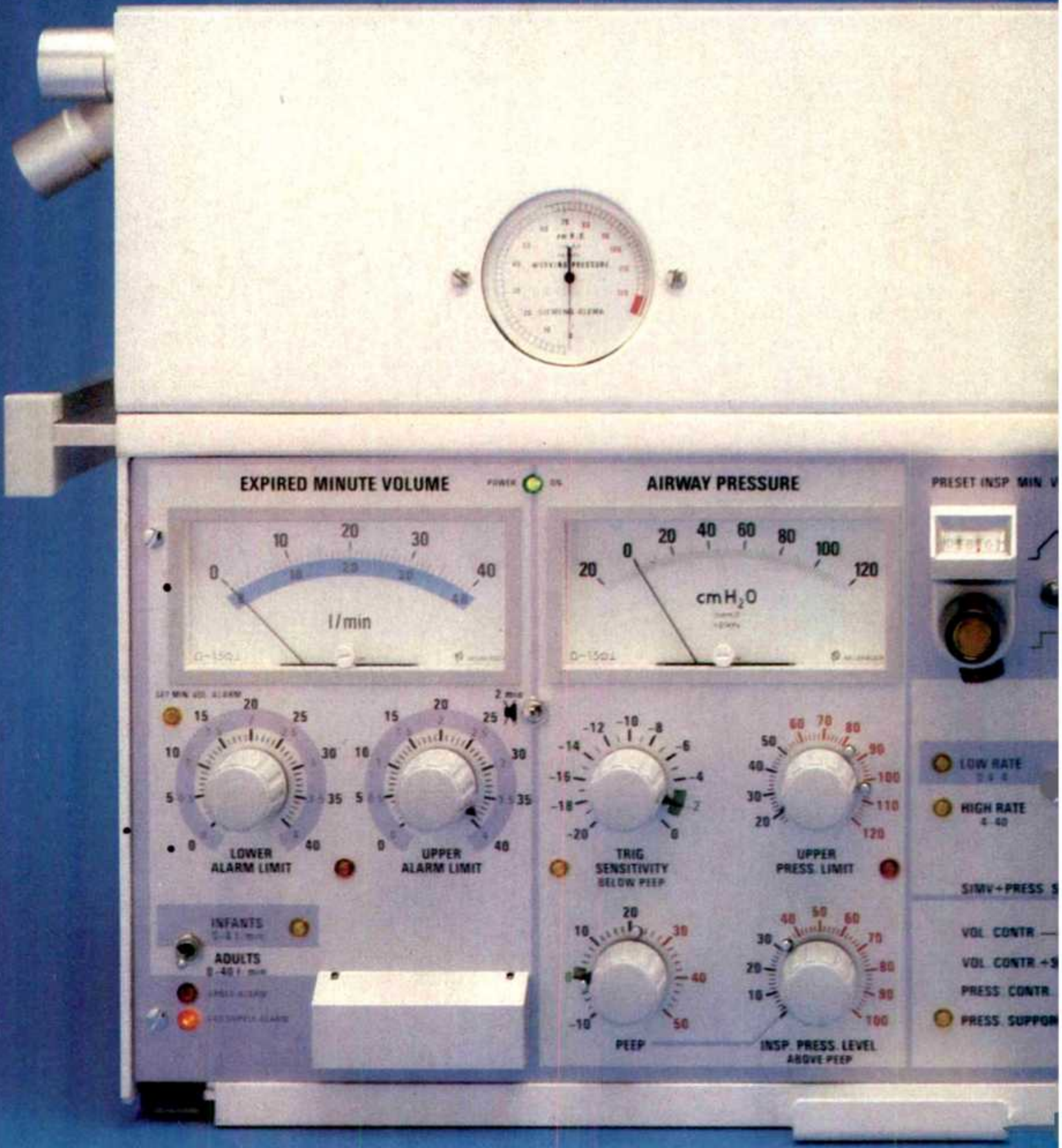
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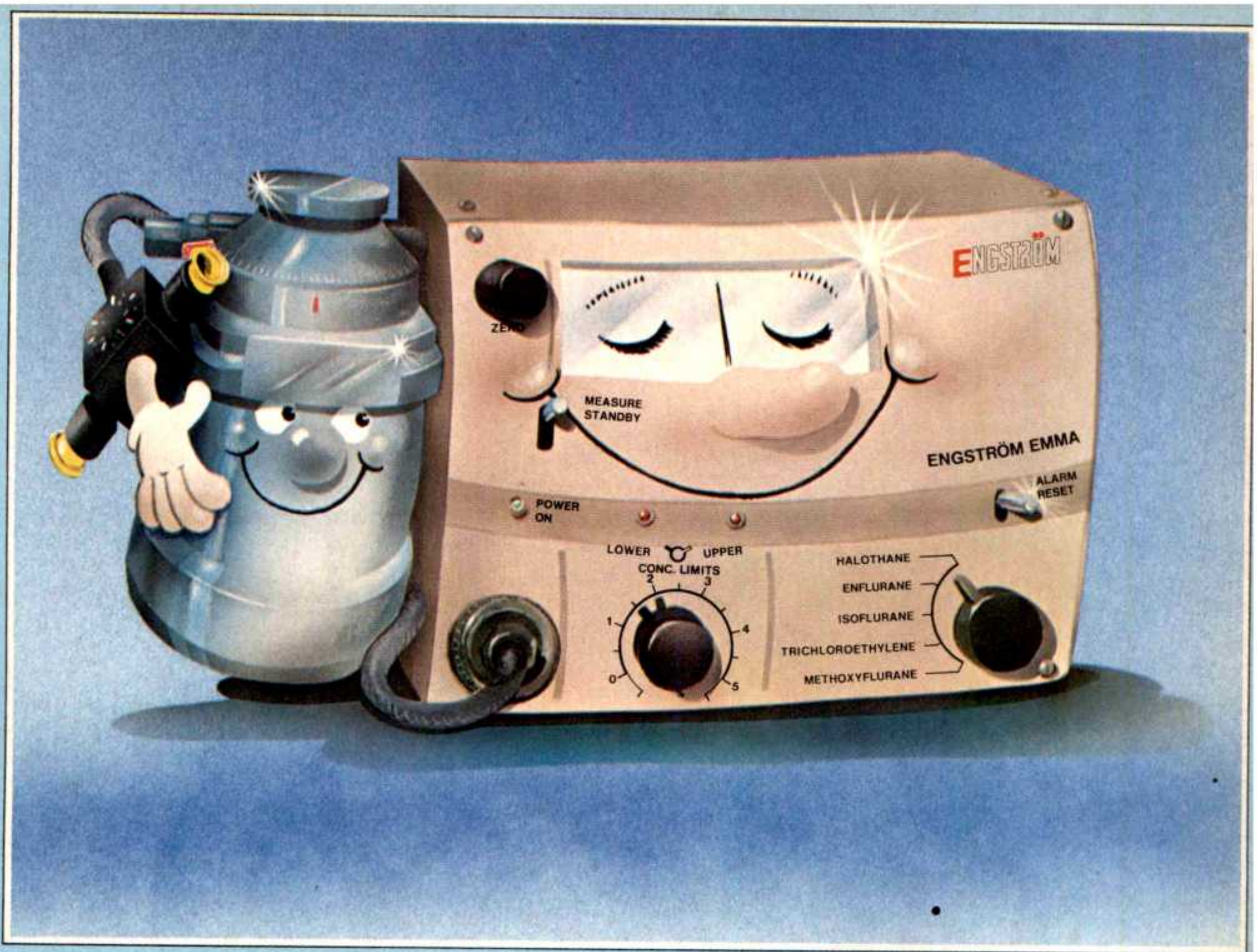

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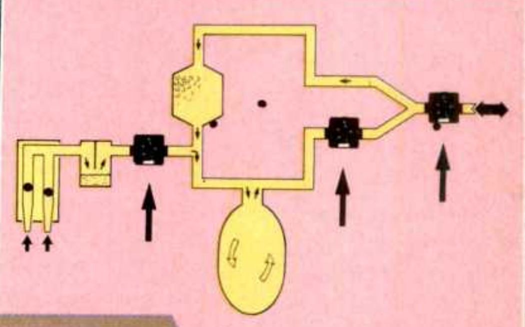

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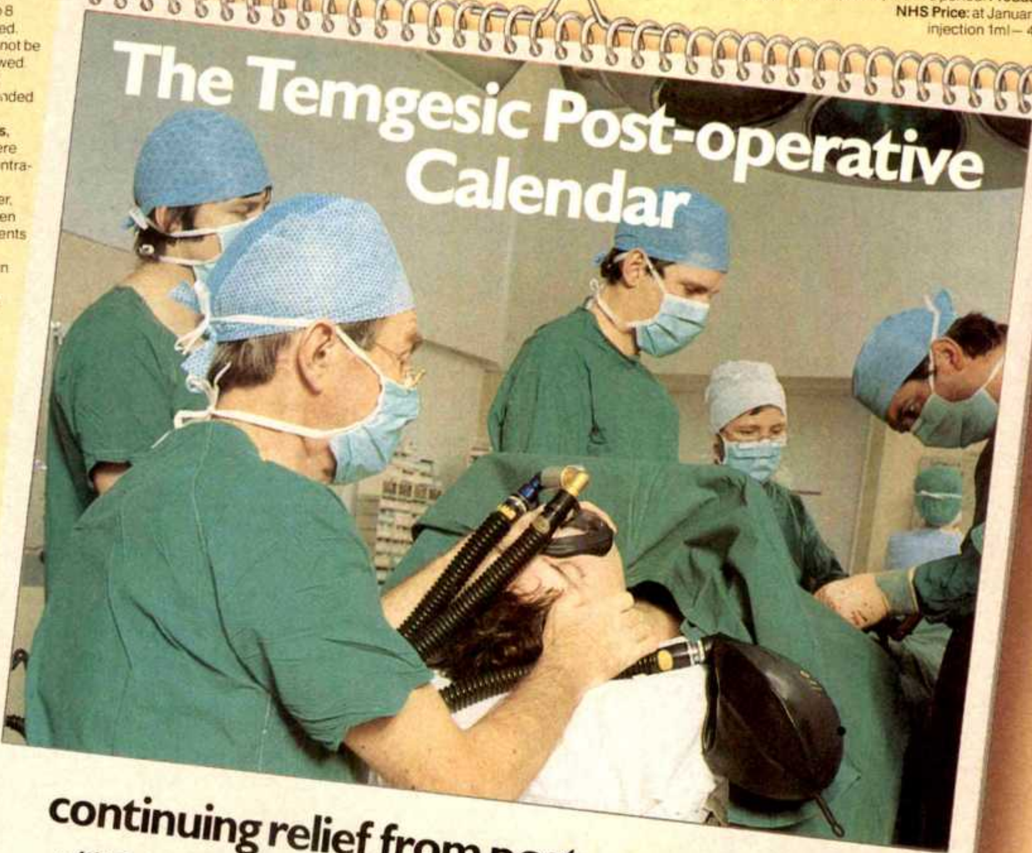

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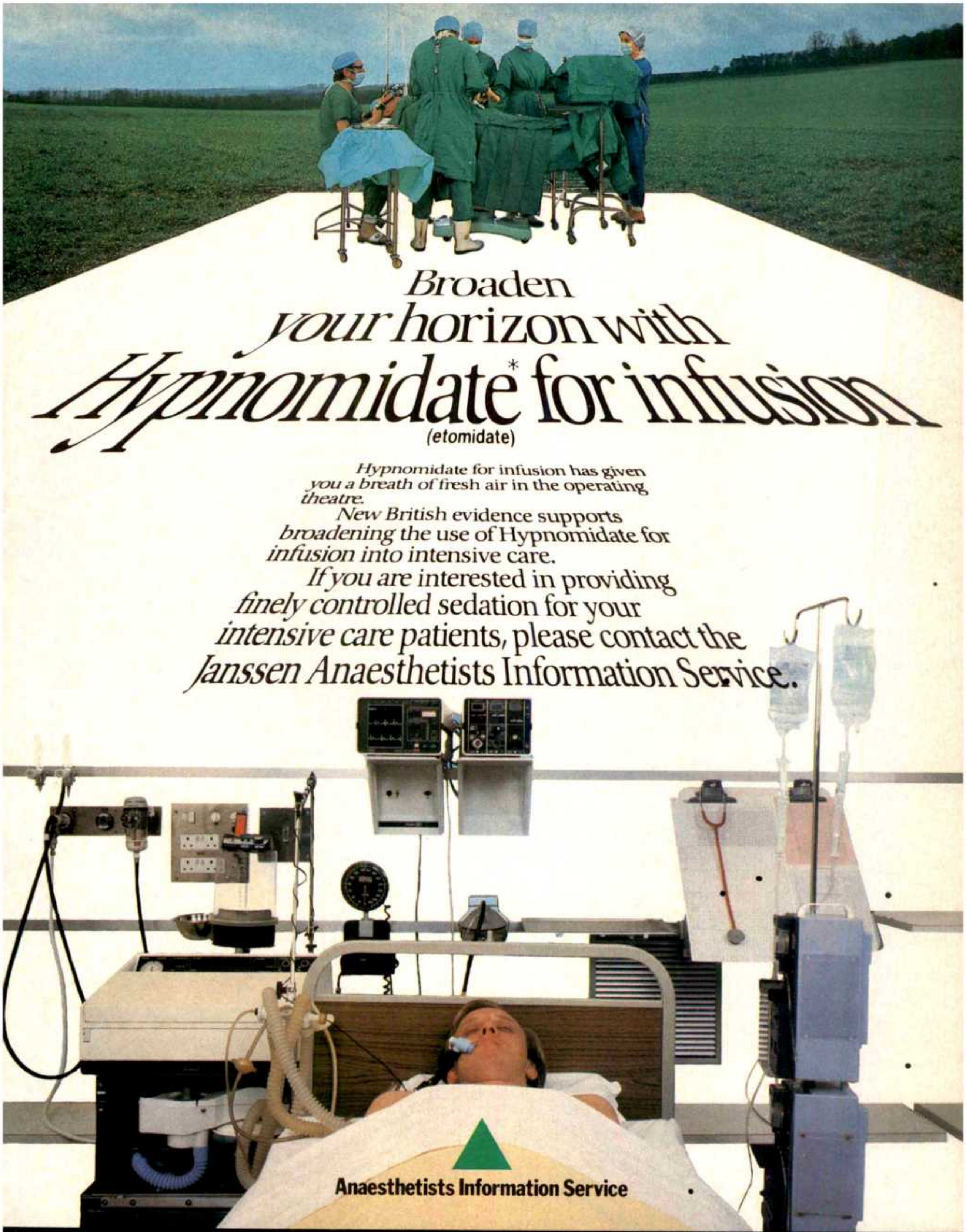
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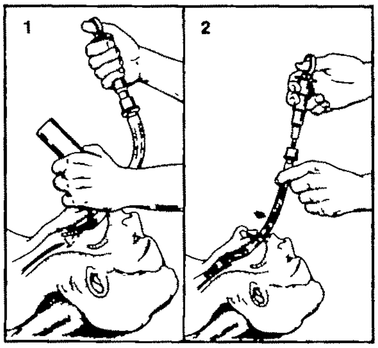

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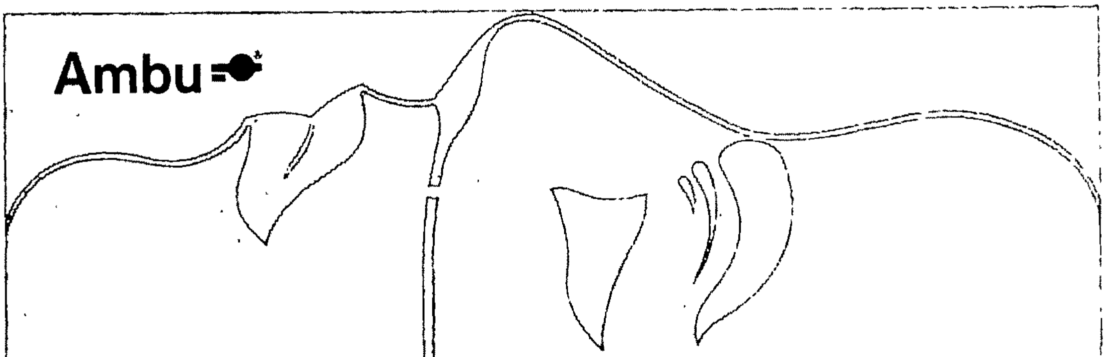

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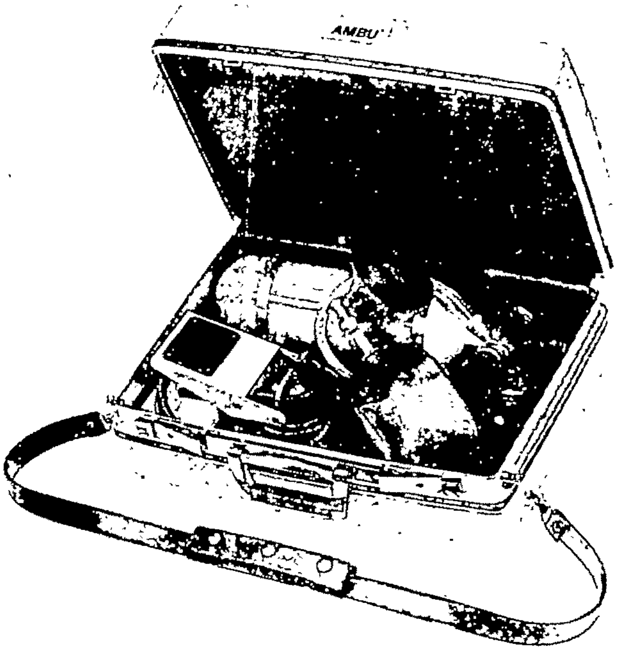

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EDITORIAL

MONITORING RESPIRATION IN THE POSTOPERATIVE PERIOD

Continuous monitoring of respiration is practised infrequently in the period after operation. Respiration is usually monitored by intermittent visual assessment in contrast to cardiovascular function, which is often monitored closely with sophisticated electronic equipment. The reasons for this disparity are unclear, since respiratory problems are common in the postoperative period. A general assumption exists that if deterioration occurs it will be sufficiently gradual to be detected before any harm results. However, recent trends in anaesthetic techniques and new observations of respiratory problems in a variety of clinical situations, suggest that this assumption may be incorrect.

In attempts to produce "stress-free" anaesthesia and to minimize the use of volatile agents, potent synthetic narcotic analgesics such as fentanyl have been used in increasing doses (Editorial, 1979). Fentanyl is generally regarded as a short-acting drug, although sensitive tests of respiratory function have shown that a modest dose of 100 μg depresses respiration to the same degree and duration as an equi-analgesic dose of morphine (Rigg and Goldsmith, 1976). Of greater concern is the observation of a "biphasic" effect with early recovery and later depression, occasionally requiring resuscitation (Adams and Pybus, 1976). Those patients likely to develop late respiratory depression are impossible to identify clinically.

The discovery of opiate receptors in the spinal cord and the analgesia provided by extradural and intrathecal narcotic analgesics, offers an interesting new dimension in the management of postoperative pain (Spence, 1980). However, as with many new techniques, the hazards soon became apparent. Delayed respiratory depression, often many hours after administration, was reported after both extradural (Christensen, 1980; Reiz and Westberg, 1980) and intrathecal use (Sidi et al., 1981). It would appear that, as with fentanyl, although the likelihood of respiratory depression is increased by a large dose or the simultaneous administration of other narcotics, susceptible patients cannot be readily identified. These techniques are often most useful in patients with pre-existing respiratory disease which may increase the hazards of any respiratory depression.

Apnoea, defined as cessation of airflow for at least 10 s, is a normal accompaniment of sleep. A normal man has between one and 25 episodes per night and a normal woman only none to five episodes. The apnoea may be of central or obstructive origin (Guilleminault, van den Hoed and Mitler, 1978). Such periods of apnoea are harmless in the majority of normal individuals, whether they occur in normal or drug-induced sleep. However, if hypoxia is present as a result of hypoventilation, lung collapse or chronic lung disease, then a profound but usually transient (and thus undetected) decrease in arterial oxygen saturation may result. Such an episode could well be a precipitating factor in postoperative myocardial infarction. The experimental evidence for this hypothesis is now emerging.

Catling and her colleagues (1980) demonstrated hypoventilation and periods of apnoea in patients receiving papaveretum, whether given by the i.m. or the i.v. route. The same group has recently demonstrated that the periods of apnoea and hypoventilation may result in a reduction in arterial oxygen saturation to less than 80% (Catley et al., 1982).

It would appear that some individuals do not respond in a normal fashion to hypoxia (Cormack, Cunningham and Gee, 1957; Hirsham et al., 1975), hypercarbia and inspiratory loading (Schiffman et al., 1980). These findings have been shown to be of relevance in the "cot-death" syndrome (Editorial, 1980) and may also be important in the late stages of chronic bronchitis and emphysema. Flenley and his colleagues (Douglas et al., 1979) have suggested that the traditional classifications of "pink-puffers" and "blue-bloaters" may be related to differing responses to hypoxia. "Blue-bloaters" have episodes of nocturnal arterial desaturation which can be both profound and prolonged, in contrast to "pink-puffers" who have no similar episodes. The frequency of blunted respiratory reflexes in the population is unknown, but the probable relevance to respiratory problems in the period following surgery is self-evident.

Snoring, the audible indication of partial upper airway obstruction during sleep, is a frequent source of humour. However, it may not be as harmless as is commonly supposed. Persistent snoring afflicts 53% of men and 38% of women at some time. The studies of Lugaresi, Coccagna and Cirignotta (1978) show that systemic and pulmonary arterial pressures increase with deepening sleep, not to the extent seen in patients with the "sleep apnoea syndrome", but in clear contrast to non-snorers. Snoring may be caused by abnormal relaxation of the pharyngeal musculature or anatomical abnormalities. The particular problem of adenoidal and tonsillar hypertrophy in children has been highlighted recently (Wilkinson et al., 1981). Again, the relevance of these observations to the postoperative period is undetermined. It would be instructive to investigate the correlation between a history of snoring and postoperative airway obstruction.

There is thus circumstantial evidence to suggest that transient respiratory disturbances may be common in the late postoperative period. Some of the new anaesthetic techniques may increase the frequency of occurrence and, in addition, some individuals may be less able to compensate for such disturbances.

How can we detect these disturbances? Hypoventilation and apnoea of either central or obstructive origin can be detected reliably (Hanning and Spence, 1982). The impedance technique is widely available and has the merit of simplicity. However, the signal is not quantitative and studies in infants show that apnoea may not be reliably detected (Southall et al., 1980). Methods which detect airflow at the mouth, such as a thermistor or capnograph, are preferable since both central and obstructive apnoea are detected. However, they are not very well tolerated and only provide a qualitative signal.

The most promising new transducer is the inductance plethysmograph (Hanning, Smith and Ledingham, 1978; Sackner, 1979). The signal is quantitative and central and obstructive apnoea can be detected. At present its use has been confined to respiratory research, but a clinical version is under development.

The purpose of monitoring should be threefold. To ensure patient safety; to determine the influence of abnormal respiratory control on the events of the postoperative period and to identify the anaesthetic and analgesic techniques which minimize respiratory disturbances.

C. D. Hanning

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The accuracy of the Scala Alternans Altera oscillotonometer was investigated by comparison with direct intra-arterial pressures. It was found that the traditional criteria for detecting systolic and diastolic pressures were in error. A slow deflation rate was essential for the accurate measurement of systolic pressure, the maximum amplitude of needle oscillation correlated closely with mean pressure, and the determination of diastolic pressure was so inaccurate as to be clinically useless. The response of the oscillotonometer was also found to be dependent upon the individual combination of oscillotonometer and patient.

Although the oscillotonometer has been in clinical use for many years, we have been unable to trace any publication which has examined its accuracy. Although standard texts (Scurr and Feldman, 1974; Sykes, Vickers and Hull, 1981) give instructions for its use, and a general description, they present little evidence of its performance. The only relatively recent publication (Corall and Strunin, 1975) investigated the effects of cuff reversal and different methods of usage in a patient assumed to be constantly normotensive.

The introduction of the oscillotonometric method is generally attributed to Von Recklinghausen, and his name appears on the dial of each instrument. His book (Von Recklinghausen, 1931) is frequently quoted as describing the technique and apparatus. However, this monograph contains no reference to either double cuffs or oscillotonometric measurements, but deals only with oscillometric determinations of arterial pressure using a single cuff. (The Scala Alternans Altera is manufactured in Germany by Speidel & Keller, and by Bosch & Sons, both of Jungingen, West Germany. Neither of these manufacturers replied to the authors' requests for information concerning the original design of the oscillotonometers manufactured today.)

The use of two cuffs to determine arterial pressure, the lower acting as a pressure pulse detector whilst the upper was slowly deflated, was reviewed by Gallavardin (1920), in his treatise "Tension Arforearm and the maincuff on the upper arm (Münzer, 1907; Pachon, 1909; Vaquez, 1909: all quoted in Gallavardin, 1920). At or about the same time double cuff systems were being described (Bergonié, 1907/08; Finck, 1912: both quoted in Gallavardin, 1920) and the overlapping of the upper and lower cuffs was suggested by Gallavardin in 1922. However, we have been unable to trace any original articles describing the double aneroid mechanism with a controlled leak between the two chambers as incorporated in the modern oscillotonometers.

There is still controversy as to exactly how the oscillotonometer should be used, and considerable disagreement exists over the criteria for detecting systolic and diastolic pressures. The commonest criteria in clinical use are probably those used by Corall and Strunin (1975). The systolic pressure is detected by inflating the double cuff to greater than systolic pressure, opening the needle valve on the instrument case, pulling the lever over until the cuff pressure decreases sufficiently to cause a "definite increase" in "needle oscillations" and then releasing the lever to read the upper cuff pressure. The diastolic pressure is similarly detected when the "needle oscillations" show "a sudden and definite decrease".

However, this definition is open to individual interpretation and does not consider the speed of deflation of the cuffs. The latter is important because the faster the rate of deflation, the greater is the decrease in cuff pressure between heart beats, and the more apparent is the change in oscillatory amplitude of the needle. Initially, these criteria were used in a few preliminary experiments, but it became apparent that the effects of observer bias in

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interpreting what was a "definite increase" or "sudden and definite decrease" in needle oscillation were considerable. When combined with changes in the speed of deflation of the cuff it was, for instance, quite easy to record systolic pressures on the oscillotonometer which varied from just below the true intra-arterial systolic pressure to just above the true intra-arterial mean pressure.

Consequently this project was designed with two objectives. First, to provide an assessment of the overall accuracy that can be achieved by the instrument in clinical practice and, second, to define more exact criteria with precise end-points and to examine the factors in both the patient and oscillotonometer which affect its performance. For convenience the paper is divided into those two sections.

ACCURACY OF THE OSCILLOTONOMETER IN CLINICAL PRACTICE

There were two objectives to this study: first, to determine the mean calibration of the oscillotonometer by comparison with direct intra-arterial pressures and, second, to produce confidence limits for the oscillotonometer taking the intra-arterial pressure readings as the standard.

Measurements were made in 11 patients undergoing major arterial or middle ear surgery providing a range of systolic pressures from 50 to 210 mm Hg and of diastolic pressures from 30 to 110 mm Hg.

Details of the oscillotonometer

The oscillotonometer used in the experiments was an Altera model manufactured by SK of Germany. It was chosen because of its accuracy when compared statically against a mercury manometer and the low degree of frictional resistance in its mechanism. Static pressures given by this oscillotonometer fitted the regression:

$$y = (1.03x - 2.15)\text{ mm Hg with } r = 0.9998$$

where y = oscillotonometer scale reading and x = manometer reading. The 95% confidence limits for the observations about the regression were ±4.0 mm Hg throughout the range 0–300 mm Hg.

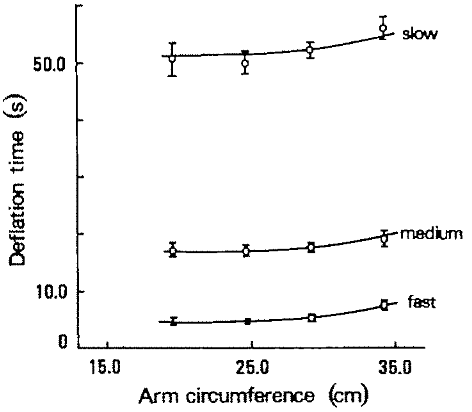


FIG. 1. Effect of arm diameter on cuff deflation time measured from 200 to 100 mm Hg after an initial inflation to 250 mm Hg. Mean ± 2 SEM, $n = 10$.

Oscillotonometers have a needle valve integral with a knurled knob with which to alter the rate of deflation of the cuffs when the lever on the valve case is pulled against its spring. For these experiments the oscillotonometer was modified so that instead of the variable needle valve one of three fixed aperture nozzles could be chosen. The aperture sizes were selected from preliminary results to produce a good range of readings, and also to span the range of deflation rates encountered in clinical use. The deflation rates using these nozzles were compared by inflating the cuffs to 250 mm Hg, deflating through the nozzle by pulling over the lever in the normal way and timing by stop watch the period of decrease from 200 mm Hg to 100 mm Hg as measured on the oscillotonometer scale. This was done with several cylinders of different circumferences acting as dummy arms and the nozzle characteristics are shown in figure 1. There were three mean deflation times of 5.0 s (fast), 17.5 s (medium) and 52.0 s (slow). The arm circumferences of the 11 patients ranged from 25 to 34 cm. There was a weak variation in deflation time with arm circumference as a result of the non-linear relationship between internal pressure and radius in an annular bag and the fact that the deflation time produced by free exhaust from a fixed aperture nozzle is dependent upon the pressure difference across it. It should be emphasized that there was no attempt to achieve *steady* deflation rates, but these accurately reproducible ones corresponded exactly with the oscillotonometer needle valve being in a given angular position.

To obviate errors from differences in arterial pressure between one arm and the other in each patient, the oscillotonometer cuff was always placed on the same arm as the arterial cannula. During surgery the cuff was surrounded by rigid arm protectors to prevent accidental displacement or compression by the theatre staff and surgeons.

The arterial pressure monitoring system

Direct arterial pressures were recorded from a Hewlett–Packard 78205 pressure module with a

Gould–Statham P23Ia transducer. The system had an amplitude–frequency response flat (±5%) to 25 Hz when connected to the patient by Vygon manometer tubing (120 cm) and an 18-gauge Teflon Abbocath. Cannulae were placed in the radial (two patients) and brachial (nine patients) arteries. The arterial pressure measured by the transducer was displayed continuously on an oscilloscope, and a digital readout gave the beat-to-beat values of systolic, diastolic and mean arterial pressures. Before and after each set of recordings on a patient the static calibration of the pressure transducer was tested to 250 mm Hg against the oscillotonometer and they were always in agreement to within ±3 mm Hg.

The method of comparison of oscillotonometer and arterial line pressures

To take a reading the cuff was inflated to greater than systolic pressure, causing the arterial line pressure signal trace to disappear from the oscilloscope screen. With the appropriate nozzle fitted the valve lever was pulled over to allow the upper cuff to deflate. When the required perturbation of the oscillotonometer needle was seen the lever was released to read the upper cuff pressure. The cuff was then allowed to deflate rapidly to atmospheric pressure by decoupling it from the oscillotonometer and after the arterial trace on the oscilloscope had been stable for a few beats the particular pressure required was read from the digital display. The objective of this technique was to decrease the time lag between the two readings and minimize the errors caused by true swings in arterial pressure occurring in that interval. Three comparisons were made of oscillotonometer and arterial pressure recordings at each of the three deflation rates:

(1) The upper cuff pressure during deflation (as measured on the oscillotonometer by release of the lever) at which the first definite "change in character" of the oscillotonometer needle swing occurred was correlated with the systolic intra-arterial pressure. The justification for doing this is discussed in the second part of the study.

(2) The upper cuff pressure (as measured on the oscillotonometer by release of the lever) at which the maximum amplitude of needle swing occurred was correlated with the mean intra-arterial pressure.

(3) The upper cuff pressure (as measured on the oscillotonometer by release of the lever) at which the amplitude of needle swing decreased markedly was correlated with diastolic intra-arterial pressure.

The first two comparisons define new criteria for the oscillotonometer with well-recognized end-points, whereas the third comparison follows that of Corall and Strunin (1975). The regression lines of these comparisons were calculated using the standard least squares technique with arterial pressure as the independent variable.

The confidence limits representing the range of *individual* oscillotonometer readings one would expect to find at a given value of arterial pressure (x_0) on 95% of occasions were calculated by application of the expression (Ryan, Joiner and Ryan, 1976):

95% confidence limits at x_0

$$= y_{\text{pred}} \pm t_{[(n-2),\,(0.05)]} \sqrt{S^2 \left[1 + \frac{1}{n} + \frac{(x_0 - \bar{x})^2}{\Sigma\,(x - \bar{x})^2}\right]}$$

where γ_{pred} = predicted value of γ at χ_0 from least squares regression; $S^2 = [\Sigma(y - y_{\text{pred}})^2]/(n-2)$; γ = observed y at x; $\bar{x} = 1/n(\Sigma x)$. This was done using a Minitab II subroutine (Ryan, Joiner and Ryan, 1976) on a Honeywell Model 68 DPS computer with a Multics operating system at the University of Bristol Computing Centre.

Results

The results of nine comparisons of oscillotonometer against intra-arterial pressure are shown in figures 2–7. There was no significant difference between the slow and medium deflation rates in the detection of mean pressure and among slow, medium and fast deflation rates in the detection of diastolic pressures. Consequently these sets of results were pooled and analysed together.

Shown on each of figures 2–7 is the least squares regression line and the 95% confidence limits for a single prediction of true arterial pressure by the oscillotonometer. Above each of the graphs is a statistical error plot of residual error ($y - y_{\text{pred}}$) against y_{pred}, which justifies the type of statistical analysis used (Petrie, 1978). This is considered later in the discussion.

FACTORS AFFECTING THE PERFORMANCE OF THE OSCILLOTONOMETER

The details of the pressure connections of the oscillotonometer are well known and are reproduced in figure 8, for convenience of reference.

The activating pressure signals

The nature of the pressure wave signals in the upper and lower cuffs which activated the oscillo-

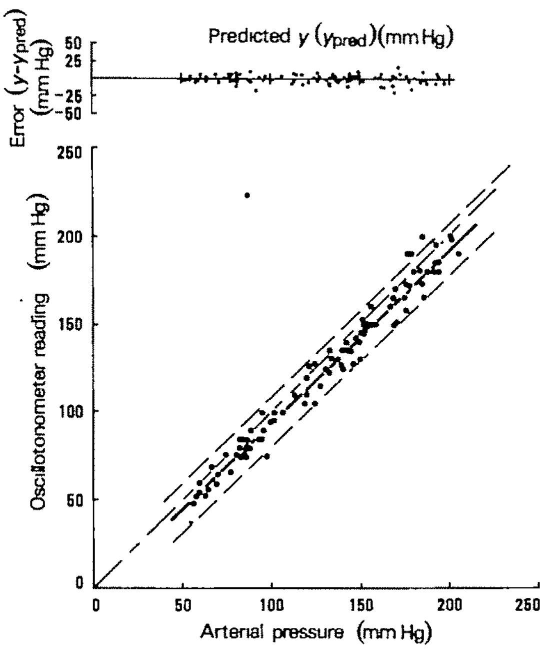


FIG. 2. Systolic pressure detection at slow deflation rate. $y = -3.69 + 0.979x$; $r = 0.986$; $n = 92$. 95% Confidence limits at $\bar{x} = \pm 13.7$ mm Hg. Mean heart rate = 69.4 beat min^{-1} (SD = 9.8). ——= regression line; — — — = 95% confidence limits; — - — - = line of indentity.

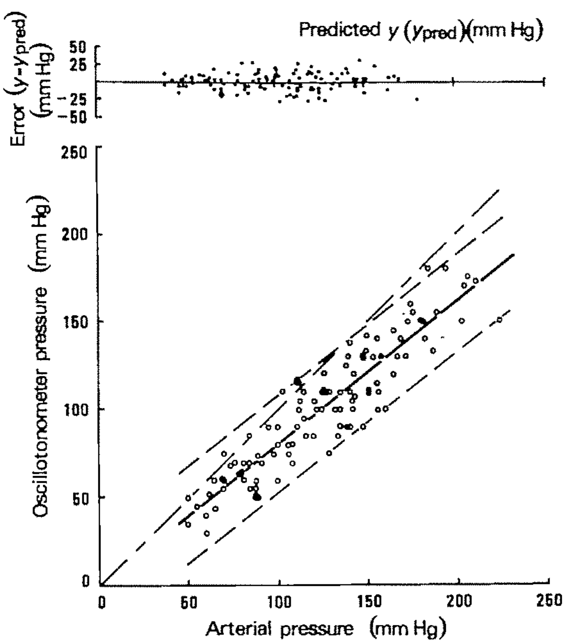


FIG. 4. Systolic pressure detection at fast deflation rate. $y = -1.02 + 0.808x$; $r = 0.918$; $n = 106$. 95% Confidence limits at $\bar{x} = \pm 27.8$ mm Hg. Mean heart rate = 70.1 beat min^{-1} (SD = 10.0). ——= regression line; — — — = 95% confidence limits; — - — - = line of identity.

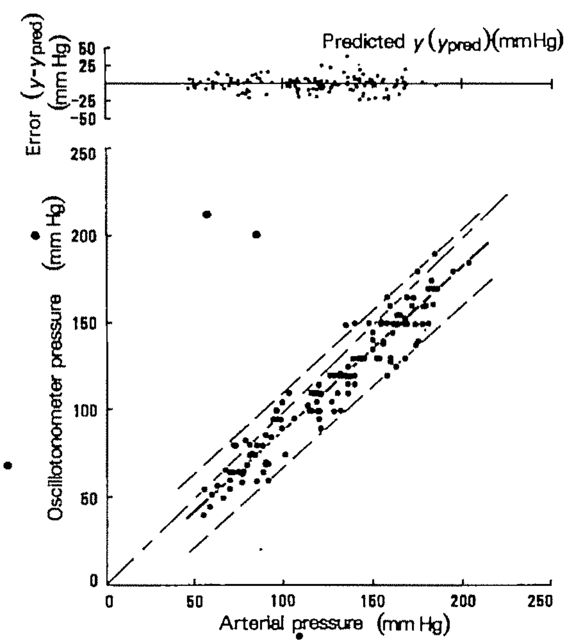


FIG. 3. Systolic pressure detection at medium deflation rate. $y = -3.98 + 0.933x$; $r = 0.953$; $n = 132$. 95% Confidence limits at $\bar{x} = \pm 21.3$ mm Hg. Mean heart rate = 69.9 beat min^{-1} (SD = 10.2). ——= regression line; — — — = 95% confidence limits; — - — - = line of identity.

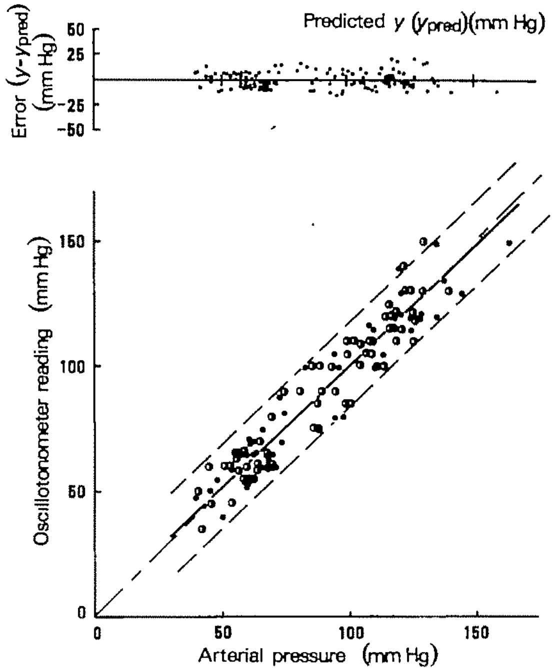


FIG. 5. Mean pressure detection at medium and slow deflation rates. $y = 2.35 + 0.965x$; $r = 0.956$; $n = 127$. 95% Confidence limits at $\bar{x} = \pm 17.3$ mm Hg. Mean heart rate = 66.2 beat min^{-1} (SD = 10.4). ● = slow deflation rate; ◑ = medium deflation rate. ——= regression line; — — — = 95% confidence limits; — - — - = line of identity.

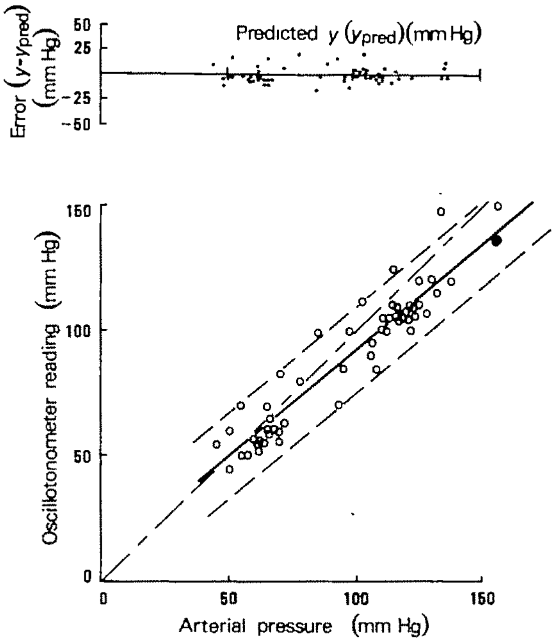


FIG. 6. Mean pressure detection at fast deflation rate. $y = 7.41 + 0.841x$; $r = 0.951$; $n = 56$. 95% Confidence limits at $\bar{x} = 16.5$ mm Hg. Mean heart rate = 69.4 beat min^{-1} (SD = 10.9). ——— = regression line; — — — = 95% confidence limits; — - — - = line of identity.

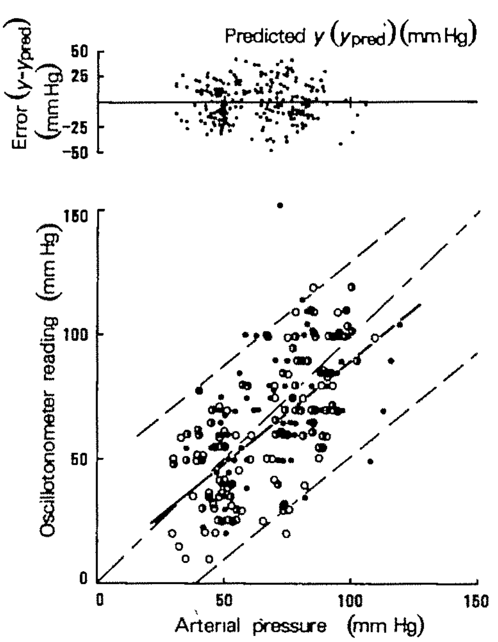
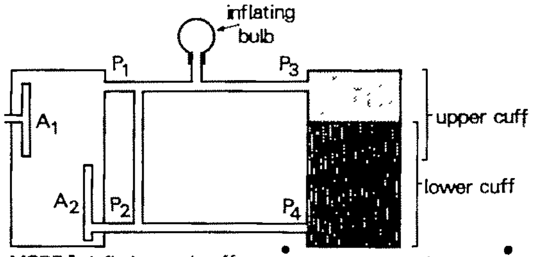


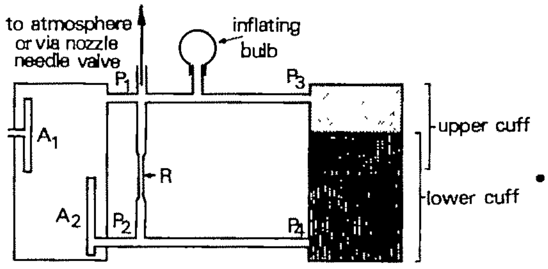
FIG. 7. Diastolic pressure detection at fast, medium and slow deflation rates. $y = 6.37 + 0.834x$, $r = 0.642$; $n = 220$. 95% Confidence limits at $\bar{x} = \pm 38.1$ mm Hg. Mean heart rate = 66.4 beat min^{-1} (SD = 8.8). ● = Slow deflation rate; ◑ = medium deflation rate; ○ = fast deflation rate. ——— = regression line; — — — = 95% confidence limits; — - — - = line of identity.

tonometer was investigated by attaching two Gould–Statham P23Ia transducers at P_3 and P_4 (fig. 8) and a Statham PM5 differential pressure transducer across positions P_1 and P_2. The two P23Ia Gould–Statham transducers had their outputs a.c.-coupled to a Mingograph chart recorder so that when the oscillotonometer was working in mode II (fig. 8) the steady decrease in cuff pressure did not produce signal drift. They did, however, accurately reproduce the shape and phase differences of pressure pulses received by the cuffs as a result of interaction with the arterial pressure pulse. The output of the PM5 transducer was recorded also. The oscillotonometer cuffs were inflated in the normal manner to greater than systolic pressure, the valve lever pulled over and the events recorded from the transducers. The results could be divided into three phases, and are shown in figure 9.

Phase 1. At greater than systolic pressures the pulse wave in the proximal arterial bed impulses against the upper cuff, producing a pulsation in the upper cuff system which is superimposed upon its steady downwards deflating pressure. This in turn transmits a reduced, in-phase signal to the lower cuff as shown at beat A of figure 9. The result is that



MODE I Inflation and cuff pressure measurement



MODE II During deflation

A_1 - low compliance aneroid

A_2 - high compliance aneroid

FIG. 8. Diagrammatic representation of oscillotonometer. R = internal resistance.

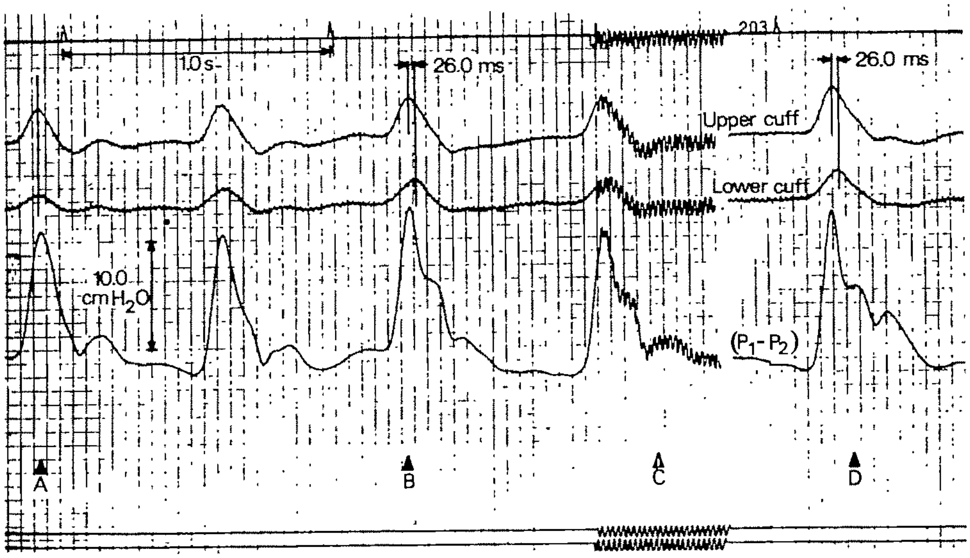


FIG. 9. Cuff pressures during "slow" deflation from above systolic pressure (see text for details).

the oscillotonometer needle decends smoothly, but with its angular velocity varying as each pulse wave is received. The magnitude of this variation appears to be dependent largely on the pulse pressure and can lead to difficulties in interpretation of the systolic point when it is identified by the criteria used by Corall and Strunin (1975).

Phase 2. As the pressure in the upper cuff continues to decrease there is, at one point, a sudden change in the smooth deflation pattern of the oscillotonometer needle. This "change in character" of the needle movement can be a sudden stop, or a fast, small-amplitude forwards or backwards movement. When this occurred there was a facility to superimpose a 50 Hz marker on all traces for 0.5 s and this is shown at C in figure 9. Between A and C there is an abrupt change in phase between the upper and lower cuff signals and a shoulder appears on the differential pressure trace. The change is complete in two beats at B (fig. 9).

This is thought to correspond to the upper cuff being just less than systolic pressure and allowing a pulse of blood beneath it to trigger the lower cuff separately. Hence, in the comparison between the oscillotonometer and intra-arterial systolic pressure values the "change in character" of the needle movement was taken as the index of the systolic point.

Phase 3. After the systolic pressure has been passed, as the upper cuff pressure is decreased further, the magnitude of both cuff signals gradually increases as, with each beat, a greater volume of blood is allowed to pass beneath the upper cuff. With this, the amplitude of the needle "swing" increases and this is reflected in the progressive distortion of the differential pressure trace. It should be noted that the phase lag between the upper and lower cuff pressures, once established as the systolic pressure is passed, never undergoes any further change. These features are shown at D (fig. 9), which is three beats on from C on the Mingograph trace, the intervening signals being omitted for clarity.

As the upper cuff pressure continues to decrease, the amplitude of the needle swing steadily increases to a maximum (taken as corresponding to mean pressure), and then declines. There are then no further definitive "end-points" as the magnitude of both the upper and lower cuff and differential signals decrease progressively as the cuff exerts less pressure on the arm. Therefore the estimation of diastolic pressure is very uncertain.

The interaction between the patient and oscillotonometer

Initial experiments with several oscillotonometers indicated that the magnitude both of the "change in character" of the motion of the needle which indicated systolic pressure and of the maximum amplitude of swing varied considerably depending on the combination of oscillotonometer and patient. Therefore, it was decided to investigate whether or not there could be variations both in the exciting signals produced by a patient's pressure pulse and in the response of the oscillotonometer to those signals. This was done in three sets of measurements.

Measurement of inherent damping capacity. The oscillotonometer was set up as in figure 8, with the valve lever pulled over (Mode II, but with the outlet to atmosphere occluded), pressurized to 200 mm Hg and the cuff struck a rapid blow to give a rise-time similar to that of the arterial pulse wave. The response from the Statham PM5 differential transducer applied across P_1 and P_2 is shown in figure 10. This demonstrates that, although the magnitude of the pressure wave decreases rapidly, the oscillotonometer is far from critically damped, the pressure trace undergoing approximately 8 cycles in 0.5 s before approaching the base line. Despite this, however, exciting impulses from the cuffs would have to appear at more than 120 per min before any beat-to-beat effects became important, and even then the amplitude of the remaining vibrations from the previous beat would be small compared with that of the new exciting signal.

Measurement of the frequency response. The oscillotonometer was first detached from the cuffs, the outlet to the upper cuff sealed, (tubing to P_3 occluded, fig. 8), and the needle valve screwed down. After pressurization of the main chamber a variable frequency constant volume pulsation was applied to the lower cuff inlet (at P_4, fig. 8) and the lever pulled over. This exciting signal was provided from a diaphragm loudspeaker powered by a Ling Dynamic Systems oscillator and power amplifier (TPO 25) and vibrator (Type 110, 100 series), the displacement of the central loudspeaker drive being displayed on an oscilloscope to ensure a constant amplitude over the frequency range investigated.

Eleven oscillotonometers used in two Bristol hospitals were tested in this way at mean chamber pressures of 120 and 250 mm Hg. As the frequency was gradually increased, visual measurements of needle amplitude were made with callipers. A typical response curve (that of the oscillotonometer used in the first part of this paper) is shown in figure 11.

Two of the 11 oscillotonometers tested exhibited two resonance peaks and, under given conditions, this is to be expected from a system with two aneroids of differing compliance. In both these oscillotonometers the occurrence of a double peak was dependent on the mean pressure of the main chamber and in neither was it present above 130 mm Hg. The other nine oscillotonometers exhibited only a single resonance peak. The fundamental frequency in the 11 machines tested had a mean of 19.1 Hz (SD 7.8 Hz) and an overall range of 8.3–37.0 Hz.

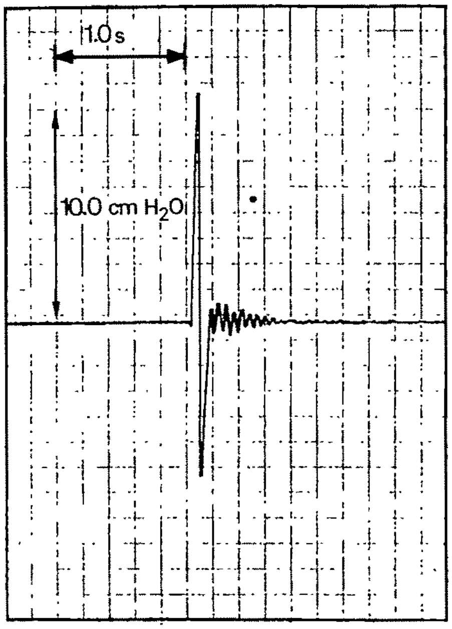


FIG. 10. Response of the oscillotonometer ($P_1 - P_2$) to a single pressure impulse.

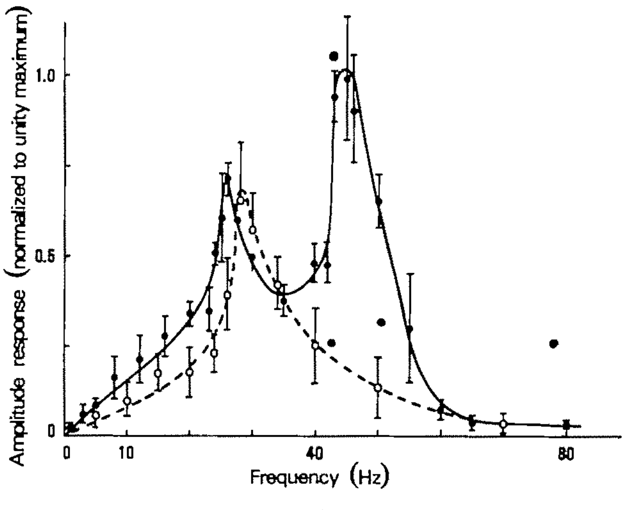


FIG. 11. Frequency response of oscillotonometer to a fixed amplitude, sinusoidal volume exciting signal with variable frequency. —— = Pressurized to 120 mm Hg; - - - pressurized to 250 mm Hg. Error bars show 95% confidence limits where $n = 6$ at each point.

Measurement of the characteristics of the exciting signals. The oscillotonometer and cuff used in the first study described in this paper were used on 29 volunteers with a mean age of 38.7 yr (SD 19.2, range 21–88 yr) with arms of mean circumference 26.4 cm (SD 2.8, range 18.0–31.5 cm). The Gould–Statham P23Ia transducers were attached to tappings at P_1 and P_2 (fig. 8) and their output fed into the Mingograph chart recorder. The cuff was then inflated to more than systolic pressure, allowed to deflate in the normal manner and a pressure wave tracing similar to figure 9 produced for each volunteer. For these measurements both the paper speed and trace height were increased. In each case the time-lag between the peaks of the two signals was measured graphically. The mean time-lag was found to be 40.2 ms (SD 15.8, range 25.6–110 ms). This time-lag will be strongly dependent on the individual patient's pulse wave velocity in the brachial artery. Because the first signal from the upper cuff is applied externally to the most compliant aneroid and the second signal from the lower cuff is applied internally to it, the range of exciting signals corresponds to effective exciting frequencies of 19.5–4.5 Hz respectively.

DISCUSSION

The statistical analysis applied to figures 2–7 requires the data to be adequately represented by a linear regression equation upon which lie the true mean values of the distribution of y for every value of x. This can be seen to be so by the symmetry of scatter about the regression lines plotted in figures 2–7. In addition it is necessary for each value of x to have a normal distribution of values of y from which the observed sample values of y are drawn at random and for the variance of this normal distribution to be constant for all values of x.

A corollary of the above assumptions is that the values of the residual error $(y - y_{\text{pred}})$ for different points are independently and normally distributed with zero mean and constant variance when plotted against the predicted value of $y\,(y_{\text{pred}})$. Consequently Petrie (1978) recommended that these assumptions are most easily validated by a graphical study of the residuals and it is this plot of residual error against predicted y which appears above each of the regression lines in figures 2–7.

The most significant deviation from the above theoretical model is probably the slight decrease in variance at low arterial pressures (< 70 mm Hg) in the systolic pressure plots of figures 2, 3 and 4. However this reduction is so small that no mathematical transform was found that could improve the overall distribution of the data for statistical processing. Thus, it can be concluded that the statistical theory applied will represent a robust test of the 95% confidence limits, but that the limits shown will tend to be pessimistic at low systolic pressures.

Normally the confidence limits predicted by this theory are shown as biconcave lines, but because the number of points on each of the graphs in figures 2–7 is large and the data are well distributed, the curvature is so slight that the lines appear straight. Perhaps it should also be noted that this method of comparison predicts the confidence limits for an individual oscillotonometer reading as it is taken in clinical practice rather than the 95% confidence limits of the mean of several oscillotonometer readings at a fixed arterial pressure. The 95% limits for the mean would necessarily be closer to the regression line, a reflection of the fact that individual readings are less predictable than averages.

The systolic pressure detection plots (figs 2, 3, 4) show a progressive separation from the line of identity and a widening of the 95% confidence limits as the rate of deflation increases. In practice, detecting the systolic point often requires two beats, the first to notice the change in character of the beat, the second to confirm this change. At the fast deflation rate the pressure in the upper cuff is, on average, decreasing at 20 mm Hg s^{-1} over the measured range. At a pulse rate of say 60 beat min^{-1} two extremes can occur. First, if a beat coincidentally appears just as the upper cuff pressure decreases below systolic pressure, it is recognized immediately and the lever released, then the cuff pressure reading will be close to the equality line. However, if one beat is just missed, the cuff pressure may be 20 mm Hg less than true arterial pressure before the systolic pressure is recognized and then if a further beat is required for confirmation the cuff pressure may be 40 mm Hg less than true systolic pressure before the lever is released and the cuff pressure measured. In this way the regression line for systolic pressures decreases further below the line of identity and the scatter about it is increased when a fast deflation rate is compared with a slower one.

A summary of the regression equations and sample data is given in table I.

In figures 2, 3 and 4 some points appear above the line of identity and this can be explained by either inherent errors or a true decrease in arterial pressure

TABLE I. *Regression equations between oscillotonometer values of arterial pressure* (y) *and direct arterial pressure* (x) *and sample data. *Plotted together because there is no significant difference between the regressions of the different deflation rates*

Pressure detected	Speed of cuff deflation	Regression line and Sample data	Correl. coeff. and No. points	95% Confidence bands at $\bar{x}$
Systolic	Slow	$y = -3.69 + 0.979x$ $x = 120, y = 113.8$	$r = 0.986$ $n = 92$	± 13.7 mm Hg
	Medium	$y = -3.98 + 0.933x$ $x = 120, y = 108.0$	$r = 0.953$ $n = 132$	± 21.3 mm Hg
	Fast	$y = -1.02 + 0.808x$ $x = 120, y = 95.9$	$r = 0.918$ $n = 106$	± 27.8 mm Hg
Mean	Slow and medium*	$y = 2.35 + 0.965x$ $x = 100, y = 98.9$	$r = 0.956$ $n = 127$	± 17.3 mm Hg
	Fast	$y = 7.41 + 0.841x$ $x = 100, y = 91.5$	$r = 0.951$ $n = 56$	± 16.5 mm Hg
Diastolic	Slow, medium and fast*	$y = 6.37 + 0.834x$ $x = 80, y = 73.1$	$r = 0.642$ $n = 220$	± 38.1 mm Hg

occurring between the oscillotonometer and arterial pressure recordings. Alternatively it could result from an increase in upper cuff pressure on release of the lever (see below).

It should be noted in figures 2, 3 and 4 that the lines of identity and regression lines gradually diverge as the arterial pressure increases, and this is to be expected because of the non-linear behaviour of a fixed nozzle. When the pressure difference across the nozzle is greatest it will deflate the fastest. Hence for a given nozzle or needle valve setting the deflation rate decreases and the accuracy increases as the systolic pressure it is measuring decreases.

The mean pressure plots (figs 5, 6) show a good correlation with the true arterial pressure, the medium and slow deflation rates being plotted together because of the lack of a significant difference between them. At a given pulse rate the decrease in the number of sampling beats per unit pressure change when the medium rather than the slow nozzle is used is probably compensated for by the ease of identifying the maximum amplitude of swing more easily. This is because the growth and decay of the signal gives a more easily discernible peak at the medium deflation rate. This advantage is lost at the fast deflation rate. No theoretical reason could be found for the correlation of maximum amplitude of swing with mean arterial pressure.

Detecting the diastolic pressure has no real end-point in terms of changes in pressure waves except that they decrease in amplitude as the compression on the arm is eased. This cuff pressure depends on several variables, including the initial tightness of the cuff and its exact position on the arm, and these uncertainties are reflected in the extremely wide confidence limits of ± 38.1 mm Hg.

Because the deflation rate was so crucial to the performance of the oscillotonometer, the deflation rates obtained by the use of the needle valve were investigated by allowing the cuffs to deflate around a standard arm (circumference 27 cm) after inflation to 250 mm Hg and timing the deflation period from 200 to 100 mm Hg. The results are shown in figure 12 and demonstrate that the maximum deflation rate was reached after only 30° angle of turn. It is thus clear that the confidence limits and regressions of the slow deflation speed (52 s) can be converted to those of the fast (5 s) by a turn of approximately only 26° on the needle valve.

Another factor which may affect the accuracy of the cuff pressures is the differential pressure between the two cuffs as the pressures are decreasing. This was measured by tapping at P_3 and P_4 (fig. 8) with the Gould–Statham pressure transduces and

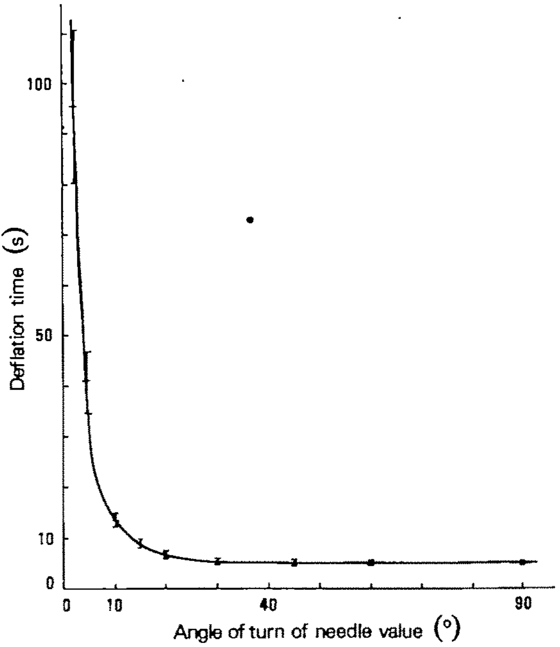


FIG. 12. Time of deflation of oscillotonometer cuff from 200 to 100 mm Hg after an initial inflation to 250 mm Hg plotted against rotational angle of needle valve. $n = 10$ at each point. Error bars = ±2 SEM; test circumference = 27.0 cm.

across P_3 and P_4 (fig. 8) with the Statham PM5 differential transducer. During deflation the upper cuff pressure was always less than the lower cuff pressure because of the choke present between the two systems. At the fast deflation rate the maximum differential pressure between the cuffs was 15.3 mm Hg and at the slow deflation rate 4.5 mm Hg. On release of the lever to take the upper cuff pressure, the upper cuff pressure increased by two-thirds of the differential pressure and the lower cuff pressure decreased by one-third. This change reflects the proportionate volumes of the cuff and oscillotonometer chambers combined. It should be noted that this change in upper cuff pressure on release of the lever would tend to push the regression line closer rather than further away from the line of identity.

The range of pulse rates in all the studies (given in figs 2–7) is so similar that it will not have affected any of the comparisons of the three deflation rates. In general, however, for a given deflation rate, pressure determinations will be more accurate the faster the pulse rate, simply because there are more signals available to be detected in a given time. This applies for all determinations whether systolic, mean or diastolic.

The regressions and confidence limits of each individual patient were compared with those shown in figures 2–7 and no significant differences were found. Hence the oscillotonometer will not "follow" a given patient's arterial pressure with tighter limits than those shown in figures 2–7.

There is a considerable overlap between the range of resonant frequencies of the oscillotonometers (8.3–37.0 Hz) and the range of effective exciting frequencies (4.5–19.5 Hz), the latter being strongly dependent on the pulse wave velocity of the individual patient. This may well explain why some oscillotonometers seem, in practice, to respond better to some patients than others. Although this interaction has an effect on the form and magnitude of the response of the oscillotonometer, it does not affect the cuff pressure at which the systolic and mean pressure end-points are determined.

CONCLUSIONS

(1) For detection of systolic pressure the first "change in character" of the deflation pattern of the oscillotonometer needle should be taken as the end-point. This is most accurately detected at a slow deflation rate or by deflating the cuffs intermittently at intervals of a few mm Hg.

(2) Mean pressure corresponds well to the maximum amplitude of the oscillotonometer swing and its accuracy is maintained at the medium deflation rate. No theoretical basis can be found for this correlation at present.

(3) The oscillotonometer is useless for the clinical determination of diastolic pressure.

(4) It is probable that the ease with which the systolic and mean pressure end-points are detected is dependent upon the individual combination of oscillotonometer and patient.

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L'OSCILLOTONOMETRE EN THEORIE ET EN PRATIQUE

RESUME

Nous avons étudié la précision de l'oscillotonomètre Scala Alternans Altera en le comparant avec la prise directe de pressions intra-artérielles. Il en est ressorti que les critères traditionnels de détection des pressions systoliques et diastoliques étaient erronés. Il est essentiel d'assurer un dégonflage lent pour mesurer avec précision la pression systolique, le maximum d'amplitude de l'oscillation de l'aiguille est étroitement corrélé à la pression moyenne, et la détermination de la pression diastolique est si imprécise qu'elle est inutilisable en clinique. La réponse de l'oscillotonomètre s'est également révélée dépendante du couplage oscillotonomètre–patient.

DIE OSZILLOTONOMETRIE IN THEORIE UND PRAXIS

ZUSAMMENFASSUNG

Die Genauigkeit des Scala Alternas Altera Oszillotonometers wurde durch Vergleich mit der direkten intraarteriellen Druckmessung untersucht. Wir fanden daß die herkömmlichen Kriterien den systolischen und diastolischen Druck ausfindig zu machen falsch sind. Ein langsames Ablassen der Luft war wesentlich für eine genaue Messung des systolischen Druckes. Die größte Amplitude der Nadelschwindung korrelierte mit dem mittleren Blutdruck, aber die Bestimmung des diastolischen Druckes war so ungenàu daß sie klinisch praktisch nutzlos ist. Es stellte sich auch heraus, daß die Reaction des Oszillotonometers von der jeweiligen Verbindung von Oszillotonometer und Patient abhängig war.

EL OSCILOTONOMETRO EN LA TEORIA Y EN LA PRACTICA

SUMARIO

Se investigó la precisión del oscilotonómetro "Scala Alternans Altera" en comparación con las presiones intraarteriales directas. Se averiguó que el criterio tradicional para la detección de las presiones sistólicas y diastólicas era erróneo. Fue esencial un régimen lento de desinflación para poder medir con precisión la presión sistólica, la ampitud máxima de la oscilación de la aguja presentó una estrecha correlación con la preción media y la determinación de la presión diastólica fue tan inexacta que clínicamente fue inservible. Se averiguó que la respuesta del oscilotonómetro fue dependiente de la combinación entre el oscilotonómetro y el paciente.

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SERUM METHIONINE AND HEPATIC ENZYME ACTIVITY IN ANAESTHETISTS EXPOSED TO NITROUS OXIDE

J. F. NUNN, N. SHARER, D. ROYSTON, R. W. E. WATTS, P. PURKISS AND H. G. WORTH

SUMMARY

Normal serum concentrations of methionine, leucine, isoleucine and valine have been found in 10 anaesthetists using nitrous oxide under their regular working conditions without scavenging of patients' exhaled gas. Mean inhaled concentrations of nitrous oxide ranged from 150 to 400 p.p.m. The results indicate either that there was no significant inhibition of methionine synthase (attributable to oxidation of vitamin B_{12} by nitrous oxide) or that methionine concentrations were maintained by dietary intake or by the alternative betaine pathway of methylation of homocysteine. In either case, anaesthetists working under these conditions should not be at risk from reduced methionine concentrations. We also report normal serum activities of aspartate transaminase and gamma glutamyl transpeptidase.

Epidemiological studies of the hazards of working in operating theatres are prone to biased reporting, but nevertheless an increased rate of abortion is a consistent finding (Vessey and Nunn, 1980) and there is some evidence that this is related to exposure to nitrous oxide (Cohen et al., 1980; Lane et al., 1980). A few hours of exposure to concentrations of nitrous oxide greater than about 1% results in oxidation of vitamin B_{12}, causing inactivation of methionine synthase, of which it is the co-factor (Deacon et al., 1978; Koblin et al., 1981). Inhibition of this enzyme seems likely to be responsible for the derangement in folate metabolism that interferes with the synthesis of thymidine (Amess et al., 1978; Chanarin, 1980).

Animals chronically exposed to lower concentrations of nitrous oxide (0.1–0.5%) have depressed hepatic methionine synthase activity (Nunn and Sharer, 1981). These concentrations are rather higher than those of time-weighted mean samples drawn from the front of masks worn by anaesthetists working without scavenging devices for 2-h periods under routine operating theatre conditions (Davenport et al., 1980). However, peak concentrations are much higher than the time-weighted mean values (Hillman et al., 1981) and may have a greater effect because of the irreversible chemical action of nitrous oxide on the cobalamin, which is in contrast to the weak reversible bonding that is characteristic of most other actions of inhalation anaesthetics. It is not known, however, whether prolonged exposure to trace concentrations of nitrous oxide has any effect on vitamin B_{12} of operating theatre staff.

The most sensitive index of the action of nitrous oxide on vitamin B_{12} is methionine synthase activity itself. However, since this is an intracellular enzyme, there are difficulties in studying its activity in operating theatre staff. We have therefore measured the serum concentration of methionine, which would tend to decrease if an enzyme involved in its synthesis were inhibited. This has already been shown to occur in rats exposed to 50% nitrous oxide (Deacon et al., 1981), and in surgical patients whose anaesthetic regimen included nitrous oxide and whose dietary intake was restricted in the perioperative period (Parry, Blackmore and Roberts, 1981; P. O. Skacel, personal communication).

In addition we measured the serum concentration of two amino acids that utilize another B_{12}-dependent enzyme (methyl malonyl CoA mutase) in their catabolism, namely isoleucine and valine. The programme used for the analysis of these amino acids allowed us to measure leucine concurrently. We also took the opportunity of measuring hepatic enzyme activities in view of reports of an increased frequency of hepatic disorders in anaesthetists (American Society of Anesthesiologists, 1974).

METHODS

Subjects

We selected 10 members of the operating theatre staff (table I) from two hospitals where we had

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already established that anaesthetists were exposed to high concentrations of nitrous oxide (Davenport et al., 1980). No scavenging systems were in use, but hospital A used a charcoal adsorption canister which removes volatile agents but not nitrous oxide. Samples were taken between 1.30 and 3.30 p.m. on Thursday of a typical working week. Control subjects were sampled simultaneously and comprised of hospital staff who did not work in an environment where anaesthetics were used. Venous blood was taken from the antecubital fossa, allowed to clot and stored at 4 °C during transport to the Clinical Research Centre.

TABLE I. *Details of subjects*

No.	Age (yr)	Sex	Grade	Exposure to nitrous oxide during previous 80 h (h)
Hospital A				
1	27	M	Technician	26
2	30	F	Sister	26
3	31	M	Anaesthetist (Reg.)	16
4	55	M	Anaesthetist (Cons.)	17
5	26	M	Anaesthetist (SHO)	16
6	20	F	Receptionist	—
7	54	M	Technician	—
8	33	F	Radiographer	—
9	60	F	Nurse	—
10	25	F	Nurse	—
Hospital B				
11	24	F	Anaesthetist (SHO)	28
12	27	M	Anaesthetist (Reg.)	10
13	46	M	Anaesthetist (Cons.)	20
14	25	F	Anaesthetist (SHO)	30
15	29	F	Anaesthetist (Reg.)	13
16	38	M	Nurse	—
17	31	F	Sister	—
18	28	F	Nurse	—
19	38	F	Sister	—
20	30	F	Nurse	—

Nitrous oxide concentrations

The mean concentration of nitrous oxide in the operating theatre atmosphere was determined using a Wright personal sampling system (Davenport et al., 1976). Samples were taken for periods of 1 h from the area of the anaesthetist's nose. Nitrous oxide was detected by mass spectrometry (Medishield multigas monitor MS2).

Amino acid analysis

Serum samples were prepared for analysis by deproteinization with an equal volume of 10% aqueous salicylsulphonic acid. Nor-leucine was added as an internal standard. Amino acid analysis was carried out using a Technicon model TSM analyser with an accelerated program designed to resolve and quantitate methionine. With this program it is possible to determine, in addition, valine, isoleucine and leucine.

RESULTS

There was no significant difference between the mean values found for the serum methionine concentration of the operating theatre staff and the control group, nor was there any degree of correlation between these values and the number of hours of exposure during the previous 3½ days (fig. 1). The other serum amino acid concentrations measured and the hepatic function enzyme activities showed no significant difference between the two groups, although the aspartate transaminase activity was slightly above the reference range for

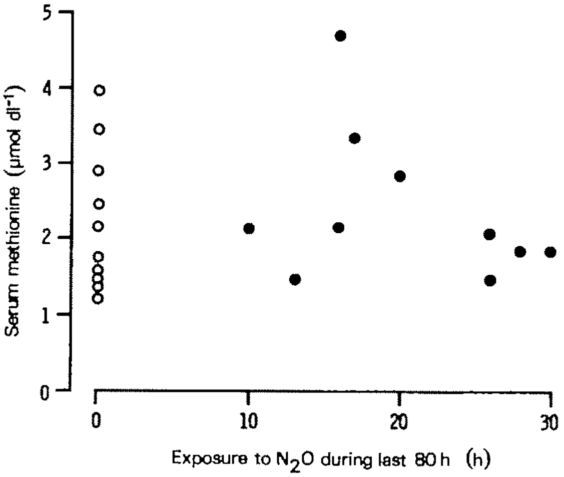

FIG. 1. Serum methionine, plotted against duration of exposure to nitrous oxide. Open circles = controls; closed circles = operating staff personnel.

one exposed subject (table II). Mean nitrous oxide concentrations in air breathed by the operating staff personnel ranged from 150 to 400 p.p.m.

DISCUSSION

This study provides no evidence of abnormality in the serum concentrations of methionine, valine, isoleucine or leucine in 10 operating theatre staff working in unscavenged environments with high ambient trace concentrations of nitrous oxide. This contrasts with the reported decreases in methionine concentrations following acute exposure to greater concentrations (Deacon et al., 1981; Parry, Blackmore and Roberts, 1981; P.O. Skacel, personal communication).

While these results are reassuring from the point of view of one potential hazard to those working in unscavenged operating theatres, it is difficult to interpret them in terms of the synthesis of methionine. This is because serum methionine is derived from at least three sources. As an essential amino acid, all the methionine in the mammalian body is ultimately of dietary origin. However, its turnover in donating methyl groups exceeds the dietary intake and therefore methionine concentrations are maintained by the remethylation of homocysteine by enzymic transfer of methyl groups from either 5-methyl tetrahydrofolate or betaine (fig. 2). Our results may mean that either methionine synthase is not significantly inhibited by the concentrations of nitrous oxide reaching the active site on the molecule under these conditions or, alternatively, that reduced methionine synthesis by this route can be compensated either by an adequate dietary intake of the amino acid or by methylation of homocysteine by the betaine pathway.

In spite of the normal amino acid concentrations

TABLE II. *Results*

	Serum amino acids (μmol dl^{-1})				Hepatic enzymes (iu litre^{-1})	
	Methionine	Valine	Isoleucine	Leucine	Gamma GT	Asp. trans.
Exposed subjects						
1	2.05	17.85	5.55	11.25	22	23
2	1.45	15.40	3.95	10.40	8	21
3	4.70	23.55	8.45	15.70	44	44
4	3.35	24.20	8.50	16.60	23	17
5	2.15	25.05	8.20	15.60	15	20
11	1.85	—	4.45	9.65	14	15
12	2.15	20.55	4.90	12.30	10	16
13	2.85	34.10	7.35	13.55	10	20
14	1.85	22.35	5.40	15.90	8	16
15	1.45	13.90	3.30	7.35	14	18
Mean	2.39	21.88	6.01	12.83	16.8	21.0
SD	1.00	6.03	1.96	3.14	10.91	8.47
SEM	0.32	2.01	0.62	0.99	3.45	2.68
Controls						
1	1.75	14.70	3.85	8.80	19	19
7	1.55	24.95	6.50	14.30	17	19
8	2.45	22.25	4.80	10.60	9	12
9	2.90	18.15	7.90	15.50	10	14
10	3.45	27.40	12.45	14.75	18	21
16	3.95	23.40	7.90	15.30	16	23
17	2.15	19.90	4.80	8.65	6	21
18	1.25	20.75	4.60	12.70	10	13
19	1.50	10.15	3.45	6.20	5	15
20	1.40	13.55	4.10	7.35	11	17
Mean	2.24	19.52	6.04	11.39	11.10	17.4
SD	0.93	5.42	2.76	3.52	4.72	3.78
SEM	0.29	1.71	0.87	1.11	1.49	1.19
t	0.35	0.90	0.03	0.97	1.51	1.23
Normal range	1.3–3.9	12–33	3.5–10.0	6.9–16.0	up to 50	10–35

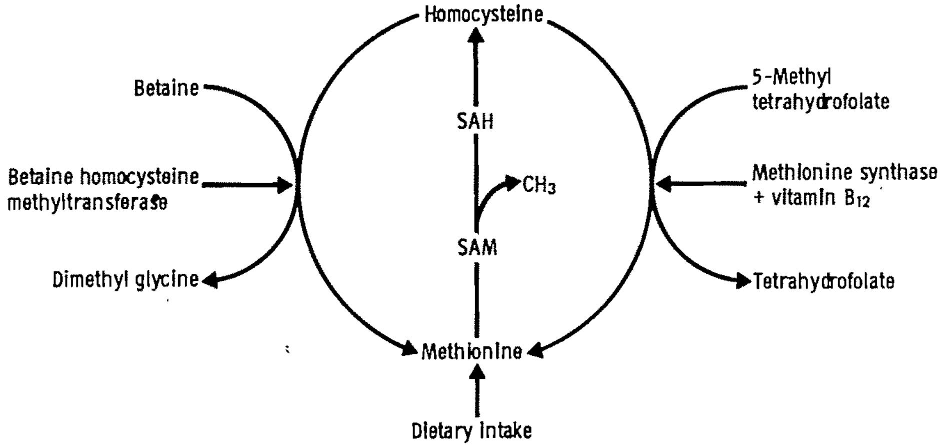
Homocysteine
SAH
CH3
SAM
Methionine
Dietary intake
Betaine
Betaine homocysteine methyltransferase
Dimethyl glycine
5-Methyl tetrahydrofolate
Methionine synthase + vitamin B12
Tetrahydrofolate

FIG. 2. Pathways in maintenance of methionine concentrations. SAM = S-adenosylmethionine; SAH = S-adenosylhomocysteine.

found in this study, there remain two special circumstances under which exposure to nitrous oxide may be dangerous and in which B_{12} inactivation is probably implicated. First, abuse by those with professional access to the gas is known to cause demyelination of the central nervous system, giving rise to a condition not unlike sub-acute combined degeneration of the cord (Layzer, 1978). This appears to be similar to a condition associated with demyelination of the cord which develops in primates exposed to nitrous oxide (Dinn et al., 1978), and which can be prevented by supplementation of the diet with methionine (Scott et al., 1981). Second, Lane and others (1980) have shown that 75% nitrous oxide causes significant fetotoxicity in rats when administered at the critical stage of pregnancy.

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CONCENTRATION SERIQUE DE METHIONINE ET ACTIVITE ENZYMATIQUE DU FOIE CHEZ LES ANESTHESISTES EXPOSES AU PROTOXYDE D'AZOTE

RESUME

Des concentrations normales de méthionine, de leucine, d'isoleucine et de valine ont été retrouvées chez 10 anesthésistes qui utilisaient du protoxyde d'azote de façon régulière dans leur travail sans évacuer les gaz expirés par le patient. Les concentrations moyennes inhalées de protoxyde d'azote allaient de 150 à 400 volumes pour 1 million. Les résultats montrent qu'il n'y a pas d'inhibition sigificative de la méthionine synthétase (qu'on pourrait attribuer à l'oxydation de la vitamine B_{12} par le protoxyde d'azote) ou que les concentrations de méthionine sont préservées par l'apport alimentaire ou par la voie alterne de la bétaine par méthylation de l'homocystéine. Dans l'un et l'autre cas, les anesthésistes qui travaillent dans ces conditions ne devraient pas courrir de risques du fait de concentrations faibles de méthionine. Nous avons également retrouvé des concentrations sériques normales d'aspartate transaminase et de gammaglutamyl transpeptidase.

SERUM METHIONIN UND LEBERENZYM-AKTIVITÄT BEI ANÄSTHESISTEN, DIE LACHGAS AUSGESETZT WAREN

ZUSAMMENFASSUNG

Normale Serumkonzentrationen von Methionin, Leuzin, Isoleuzin und Valin wurden bei 10 Anästhesisten gefunden, die bei ihrer täglichen Arbeit Lachgas benutzten ohne dass eine Gasabsaugeanlage vorhanden war. Die durchschnittlich eingeatmete Lachgasmenge reichte von 150–400 Teile pro millionen. Die Ergebnisse zeigen, dass entweder die Methionin-Synthase nicht signifikant gehemmt wird (wegen einer Oxidation des Vitamin B_{12} durch Lachgas oder aber dass die Methioninspiegel durch die Nahrungszufuhr oder durch den alternativen Betain-Stoffwechselweg durch Methylisierung von Homozystein aufrecht erhalten werden. In jedem Fall sind Anästhesisten, die unter diesen Bendingungen arbeiten nicht von erniedrigten Methioninspiegeln gefährdet. Ausserdem fanden wir normale Serumspiegel von Aspartat-Transaminase und Gammaglutamyltranspeptidase.

ACTIVIDAD LE LA METIONINA DE SUERO Y DE LA ENCIMA HEPATICA EN LOS ANESTESISTAS EXPUESTOS AL OXIDO NITROSO

SUMARIO

Se han encontrado concentraciones de metionina, leucina, isoleucina y valina en el suero de los anestesistas que usan óxido nitroso regularmente en sus ambientes de trabajo en los que no se efectúa el barrido de los gases de espiración del paciente. Las concentraciones medias de óxido nitroso inhalado oscilaron entre 150 y 400 p.p.m. Los resultados indican que no hubo una inhibición significativa de la sintasa de metionina (atribuible a la oxidación de la vitamina B_{12} por el óxido nitroso) o que las concentraciones de metionina se mantuvieron por entrada dietética o por la ruta betaina alternativa de metilación de la homocisteina. Sea como fuere, los anestesistas que trabajan bajo estas condiciones no sufren riesgo alguna a causa de las concentraciones de metionina. Asimismo informamos de que las concentraciones de aspartata trasnsaminasa y de traspeptidasa gama de glutamil en el seuro son normales.

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CONTROL OF BREATHING AFTER FENTANYL AND INNOVAR ANAESTHESIA†

K. G. SMEDSTAD AND J. R. A. RIGG

SUMMARY

Ventilation ($\dot{V}$I), end-tidal ($P'\text{CO}_2$), mixed venous ($P\bar{v}\text{CO}_2$) and the ventilatory response to carbon dioxide were measured before surgery, and during the first 4 h of recovery in 18 adult patients who underwent elective limb surgery under fentanyl or Innovar anaesthesia. End-tidal and mixed venous $P\text{CO}_2$ were increased significantly in the first 150 min after the last dose of drug ($P < 0.001$, $P < 0.01$). but had returned to control values by 4 h. Ventilation and ventilatory response to carbon dioxide were significantly depressed in all patients ($P < 0.001$), but returned to near control values at 4 h. Fentanyl and Innovar anaesthesia displaced the carbon dioxide response to the right, but no correlation was found between either the magnitude of the displacement of the response curve or the alteration in slope and the control values. This suggests that patients with a low value of $\dot{V}\text{I}/P\text{CO}_2$ are not more susceptible to the ventilatory depressant action of narcotic anaesthetics. Recovery of ventilatory responsiveness towards normal during the 4 h after anaesthesia, occurred in a graded and progressive manner; there was no evidence of a biphasic pattern of recovery.

Although Lambertsen (1960) postulated that patients with a low intrinsic ventilatory sensitivity to carbon dioxide might be more susceptible to the depressant action of narcotic drugs, recent studies in volunteer subjects have not confirmed this prediction (Rigg, 1978). However, this concept has not been studied in patients undergoing surgery and anaesthesia, although Becker and colleagues (1976) suggested that a biphasic pattern of recovery of the ventilatory response to carbon dioxide characterized the recovery of ventilatory control in patients following anaesthesia with fentanyl and Innovar.

Accordingly, the present study was designed to examine two questions: first, the relationship of the intrinsic ventilatory response to carbon dioxide to changes in ventilation and carbon dioxide responsiveness during recovery from anaesthesia with either fentanyl/nitrous oxide or Innovar/nitrous oxide; and second, the nature of the biphasic pattern of the ventilatory depression which may occur during recovery from fentanyl/nitrous oxide or Innovar /nitrous oxide anaesthesia.

PATIENTS AND METHODS

Principle

Ventilation ($\dot{V}$I), end-tidal $P\text{CO}_2$ ($P''\text{CO}_2$), mixed venous $P\text{CO}_2$ ($P\bar{v}\text{CO}_2$) and the ventilatory response to carbon dioxide ($\dot{V}\text{I}/P\text{CO}_2$) were measured before surgery, and at intervals during the period after operation, in patients having peripheral surgical procedures under either fentanyl/nitrous oxide or Innovar/nitrous oxide anaesthesia.

Subjects

Eighteen patients, aged between 19 and 60 yr, and in A.S.A. categories I or II, were studied. All patients underwent elective lower limb surgery and each gave informed consent to the study according to the procedure approved by the McMaster University Ethics Committee.

Equipment

Ventilation was measured with a Parkinson-Cowan CD 4 dry gas meter precise to ±2%. Carbon dioxide was measured with a Godart infra-red analyser, with a response time of 0.1 s and a precision of 0.2%, over the range of 0–10%. The analyser was calibrated with three gas mixtures of carbon dioxide, 40% oxygen and balance nitrogen, each of which had been analysed previously with the Lloyd Haldane apparatus. A continuous record of $P'\text{CO}_2$ and $\dot{V}$I was obtained with an Astromed pen recor-

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der. Ventilatory responses to carbon dioxide ($\dot{V}\mathrm{I}/P\mathrm{CO_2}$) were measured by the method of Read using criteria of validity described previously (Read, 1967; Rigg, Rebuck and Campbell, 1974). Oxygenated $P\bar{v}\mathrm{CO_2}$ was obtained by the equilibrium rebreathing method, before each determination of the carbon dioxide response (Hackney, Sears and Collier, 1958).

Experimental programme

Patients were allocated sequentially to two groups. Nine received fentanyl (group I) and nine Innovar (group II) as the test drug.

Group I patients were premedicated with fentanyl 1.5 μg kg^{-1} i.m. This was followed approximately 1 h later by fentanyl 4.5 μg kg^{-1} at the induction of anaesthesia. Incremental doses of fentanyl 0.75 μg kg^{-1} were administered i.v. as indicated by movement of the patient during surgery. Innovar was administered to the second group in a similar manner. All patients received thiopentone 4 mg kg^{-1} and suxamethonium 1 mg kg^{-1} at the induction of anaesthesia. Tracheal intubation was performed and ventilation of the lungs assisted by hand until spontaneous breathing resumed.

There were no significant differences between the two groups in respect of age, sex distribution, weight, height, vital capacity, duration of surgery (group 1, 53 min ± 6; group 2, 59 min ± 10) and total dose of fentanyl or Innovar administered (group 1, 454 μg ± 27; group 2, 436 μg ± 34).

Immediately following surgery patients were taken to a quiet room adjacent to the recovery room and the studies undertaken. Measurements of $\dot{V}\mathrm{I}$ $P'\mathrm{CO_2}$, $P\bar{v}\mathrm{CO_2}$ and $\Delta\dot{V}\mathrm{I}/\Delta P\mathrm{CO_2}$ were performed at 15, 45, and 90 min after the end of anaesthesia, and at 240 min after the last dose of the test drug.

Analysis of data

In order to compare the position of the response curves before and after anaesthesia, the greatest $P\mathrm{CO_2}$ value common (iso-$P\mathrm{CO_2}$) to control and post-anaesthetic response was chosen for each subject. These iso-$P\mathrm{CO_2}$ points were used to compare ventilation among the several responses of an individual patient, as a measure of the position of the response curve (fig. 1). This procedure was adopted because subjects rebreathed over widely differing carbon dioxide tensions. These iso-$P\mathrm{CO_2}$ ventilation variables were actual measurements obtained during rebreathing. Thus, errors from extrapolation of the position of the response curve which would be inevitable if a single $P\mathrm{CO_2}$ value was used for all runs in all subjects, were avoided (Rigg et al., 1977).

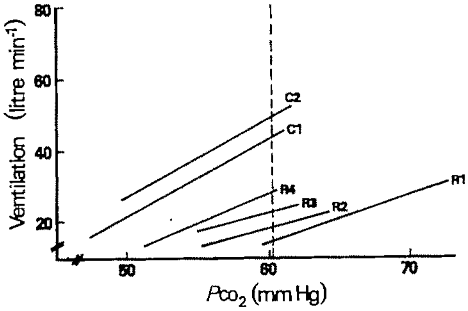

FIG. 1. Regression lines of ventilatory responses to carbon dioxide before and after Innovar/nitrous oxide anaesthesia in one subject (No. 2). (C1, C2 = control; R1 – R4 = 1st to 4th recovery responses). The vertical dashed line shows the selected iso-$P\mathrm{CO_2}$ value for the position of the curve used to compare the responses in this subject. As described in more detail in Methods, this $P\mathrm{CO_2}$ is the greatest $P\mathrm{CO_2}$ common to all the responses in an individual patient.

The slopes of all response curves were calculated by least-squares regression. The degree of ventilatory depression in the recovery period was expressed as a percentage of control. Paired *t* tests were used to determine the significance of changes induced by the drugs.

RESULTS

Profound depression of ventilation and of the ventilatory response to carbon dioxide was seen in all patients following both fentanyl and Innovar anaesthesia (table I, figs 2 and 3).

End-tidal $P\mathrm{CO_2}$ and $P\bar{v}\mathrm{CO_2}$ were increased significantly for up to 150 min after the last dose, but had virtually reattained their control values by 4 h (mean $P'\mathrm{CO_2}$ values ± SEM: control, 37.8 mm Hg ± 1.1; 15 min, 46.3 mm Hg ± 1.0 ($P < 0.001$); 240 min, 40.9 mm Hg ± 1.2 ($P > 0.05$)) (table I).

Progressive recovery of the ventilatory responsiveness towards normal was observed during the 4-h period after anaesthesia (figs 2, 3). There was no evidence of a biphasic pattern in any of the 18 patients studied. The progressive increase was found in terms of both the slope and the position of curve (fig. 1). In all subjects the depression of ventilation was greater with fentanyl than with Innovar, but this difference was not significant. Since this was consistent for all the variables studied, all the results were pooled for the analysis which compared baseline measurements before operation with

TABLE I. *Mean (± SEM) slopes of the relationships between carbon dioxide and ventilation frequency and tidal volume ($\Delta \dot{V}_I/\Delta P_{CO_2}$, $\Delta f/\Delta P_{CO_2}$ and $\Delta V_T/\Delta P_{CO_2}$) and the positions of the response curve ($\dot{V}_I$, f and V_T at iso-P_{CO_2}) before and 15, 45 and 90 min after anaesthesia and 240 min after the last dose of fentanyl (A) or Innovar (B) during anaesthesia. See text for detailed explanation of variables*

	Control		15 min		45 min		90 min		240 min	
	A	B	A	B	A	B	A	B	A	B
$\Delta \dot{V}_I/\Delta P_{CO_2}$ (litre min^{-1} mm Hg^{-1})										
Mean	2.09	1.84	0.94	1.01	1.20	1.19	1.18	1.12	1.47	1.50
SD	0.48	0.54	0.36	0.34	0.59	0.49	0.63	0.44	0.52	0.83
P			<0.001	<0.001	<0.01	<0.001	<0.01	<0.001	<0.05	n.s.
$\Delta f/\Delta P_{CO_2}$ (breath min^{-1} mm Hg^{-1})										
Mean	0.53	0.44	0.22	0.14	0.18	0.29	0.31	0.31	0.46	0.25
SD	0.27	0.24	0.08	0.27	0.20	0.30	0.25	0.49	0.61	0.23
P			<0.02	<0.05	<0.01	n.s	n.s	n.s	n.s.	n.s.
$\Delta V_T/\Delta P_{CO_2}$ (litre mm Hg^{-1})										
Mean	0.046	0.059	0.040	0.057	0.055	0.056	0.042	0.053	0.052	0.062
SD	0.016	0.034	0.017	0.036	0.013	0.644	0.018	0.033	0.024	0.033
P			n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$\dot{V}_I$ at iso-P_{CO_2} (litre min^{-1})										
Mean	47.43	70.48	22.51	20.59	25.87	22.12	26.56	23.91	32.48	30.39
SD	13.77	9.81	9.28	7.02	8.65	10.45	8.68	8.81	9.73	14.56
P			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05
f at iso-P_{CO_2} (breath min^{-1})										
Mean	22.58	18.99	14.98	15.42	15.50	14.93	16.67	15.46	19.53	18.70
SD	6.72	3.35	3.48	2.72	3.91	2.90	3.97	3.14	4.35	3.15
P			<0.001	<0.01	<0.001	<0.05	<0.001	<0.01	n.s.	n.s.
V_T at iso-P_{CO_2} (litre)										
Mean	2.12	2.21	1.54	1.36	1.70	1.52	1.63	1.61	1.70	1.66
SD	0.65	0.72	0.59	0.51	0.53	0.66	0.55	0.69	0.55	0.79
P			<0.01	<0.001	<0.01	<0.01	<0.01	<0.01	<0.01	<0.02

recovery measurements.

No relationship was demonstrated between the baseline carbon dioxide responses (slope or position) and the magnitude of the change in any ventilatory variable measured during recovery from fentanyl or Innovar anaesthesia (fig. 4, upper and middle panels). This absence of any correlation was confirmed further when corrections were made for differences in lung size (vital capacity) among patients studied (fig. 4, lower panel).

DISCUSSION

These studies confirm several earlier reports that fentanyl and Innovar cause profound and prolonged depression of breathing in the period after operation (Harper et al., 1976; Vejlsted, Hansen and Jacobsen, 1977). In addition these studies in patients confirm our earlier observations in volunteer adults that the magnitude of the depression of ventilation is not increased in subjects in whom intrinsic ventilatory sensitivity is low (Rigg and Goldsmith, 1976; Rigg, 1978).

Vital capacity is a recognized determinant of the slope of the ventilatory response to carbon dioxide (Avery et al., 1963; Rebuck et al., 1974; Irsigler, 1976). When the present results were corrected for the size of the lung by expressing the ventilatory variables as a percent of vital capacity, there remained no apparent relationship between control measurements and changes in these variables after

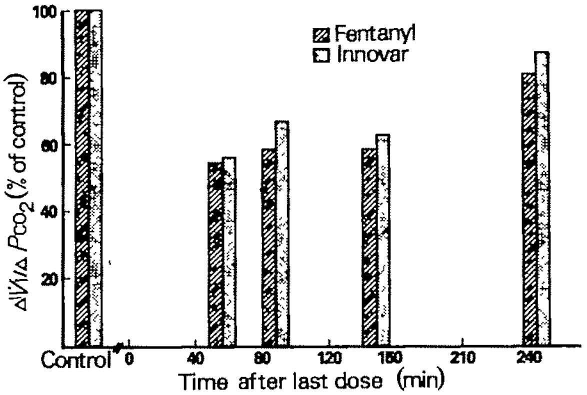

FIG. 2. Slope of ventilatory response to carbon dioxide, $\Delta\dot{V}I/\Delta PCO_2$, (expressed as % of control values) before and during recovery from fentanyl and Innovar anaesthesia. Each bar is the mean of all results in each group at the time. Ventilation is depressed significantly ($P < 0.001$) at 45, 90 and 150 min, but not at 240 min.

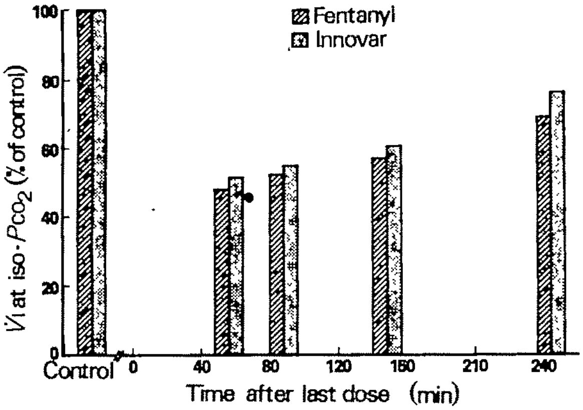

FIG. 3. Ventilation at iso-PCO_2 during rebreathing (see text for detailed explanation) (expressed as % of control), before and during recovery from fentanyl and Innovar anaesthesia. Each bar is the mean of all results in each group at that time. Depression of $\dot{V}I$ at iso-PCO_2 is very significant at 45, 90 and 150 min after drug administration ($P < 0.001$).

fentanyl or Innovar anaesthesia.

Becker and colleagues (1976) reported that, following anaesthesia using Innovar or fentanyl, marked respiratory depression was seen immediately after operation with recovery to almost 100% of control within 2 h after the last dose of narcotic. These authors then observed another decrease in ventilatory responsiveness, $\Delta\dot{V}I/\Delta PCO_2$ decreasing to as little as 50% of control at 150 min before a gradual and progressive return towards control at 4 h. They termed this phenomenon the "biphasic" pattern of recovery of ventilatory response to carbon

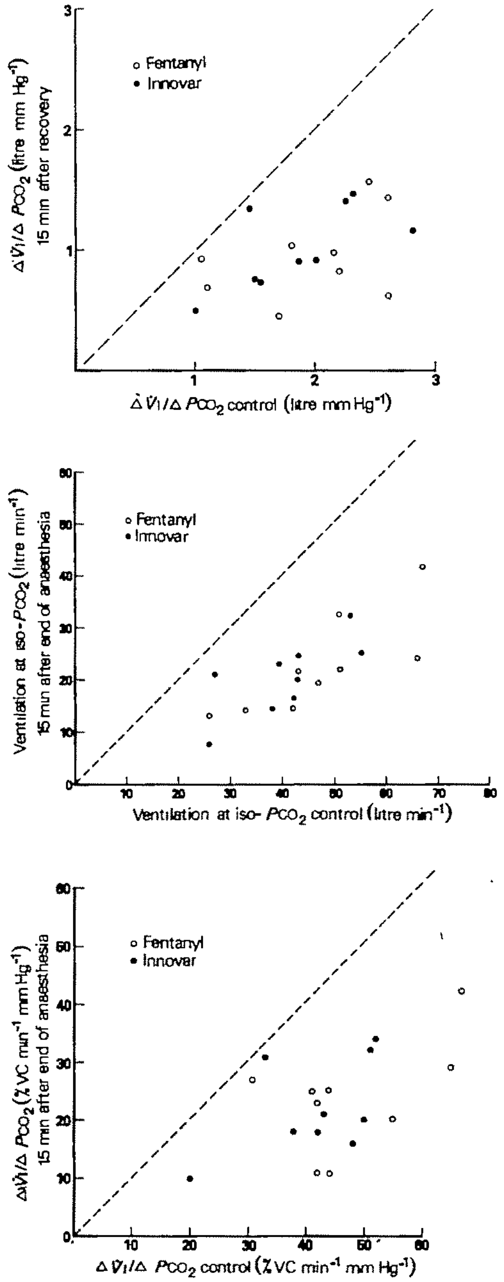

FIG. 4. Upper panel: $\Delta\dot{V}I/\Delta PCO_2$, control, plotted against $\Delta\dot{V}I/\Delta PCO_2$ at 15 min after beginning of recovery. Middle panel: iso-PCO_2 ventilation during rebreathing, control, plotted against iso-PCO_2 ventilation during rebreathing at 15 min after beginning of recovery. Lower panel: $\Delta\dot{V}I/\Delta PCO_2$, control, plotted against $\Delta\dot{V}I/\Delta PCO_2$, 15 min after beginning of recovery, both variables expressed as per cent of VC. In each panel the dashed line is the line of identity.

dioxide after fentanyl and Innovar anaesthesia.

The present results are at variance with those of Becker and co-workers (1976), since all of the patients in the present investigation showed a progressive and relatively constant rate of recovery of their ventilatory responsiveness towards normal. Hug and McClain (1980) in a similar study also reported a progressive recovery of ventilatory responsiveness following narcotic anaesthesia supplemented with enflurane and nitrous oxide in oxygen.

How can these apparently conflicting observations be reconciled? One possible explanation is based upon observations on the pharmacokinetics of fentanyl (Stoeckel, Hengstmann and Schuttler, 1979). These investigators demonstrated small increases in plasma fentanyl concentrations during the elimination phase, which they attributed to enterosystemic recirculation. They postulated that these increases reflected parallel changes in the brain and could account for the biphasic pattern of recovery of ventilatory responsiveness.

Alternatively, the difference between the study of Becker and colleagues (1976) and the present investigation may have a physiological rather than a pharmacological basis. There are two reasons for this. First, the magnitude of the small increase in plasma fentanyl concentration reported during the elimination phase in pharmacokinetic studies is small (less than 5% of the injected dose), transient, and has only been reported at plasma fentanyl concentrations substantially less than threshold concentrations for ventilatory depression in anaesthetized dogs (Murphy, Olson and Hug, 1979). More importantly, in the study in which the transient increases in plasma fentanyl concentration were found, there were no reports of any associated changes in ventilation (Stoeckel, Hengstmann and Schuttler, 1979). Second, the study of Becker and co-workers was carried out in the recovery room, where it is common practice for staff to stimulate drowsy patients vigorously during the early part of their recovery. In contrast, the present studies were conducted in a quiet room adjacent to the recovery room, in the presence of only one or two investigators.

At all times in the present study, quiet conditions were maintained. This procedure was deliberately established as part of the programme in view of the known effects of stimulation on the ventilatory reponse to carbon dioxide (Gautier, 1969; Rigg et al., 1977). Thus, it is possible that the biphasic pattern of recovery (Becker et al., 1976) and the absence of such a pattern in the present study are a consequence of the different laboratory conditions at the time of study.

An important clinical implication of this study is that preoperative determination of ventilatory response to carbon dioxide has no predictive value in assessing susceptibility to post-anaesthetic ventilatory depression. However, since respiratory depression may persist for up to 4 h after these drugs have been given, a clinical evaluation of the adequacy of respiration should always precede further administration of narcotics to patients who have been given fentanyl or Innovar as part of the anaesthetic technique.

ACKNOWLEDGEMENTS

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CONTROLE VENTILATOIRE APRES ANESTHESIE AU FENTANYL ET A L'INNOVAR

RESUME

Nous avons mesuré la ventilation ($\dot{V}\text{I}$), la pression partielle de dioxyde de carbone en fin d'expiration ($P\text{E}'_{CO_2}$) et dans le sang veineux mêlé ($P\bar{v}_{CO_2}$) ainsi que la réponse ventilatoire au dioxyde de carbone avant la chirurgie et pendant les premières 4 h du réveil chez 18 patients adultes qui subissaient une chirurgie règlée d'un membre avec une anesthésie au fentanyl ou à l'Innovar (association fentanyl–dropéridol). Les P_{CO_2} de fin d'expiration et dans le sang veineux mêlé étaient significativement augmentées pendant les premières 150 min suivant la dernière injection de produit ($P < 0{,}001$, $P < 0{,}01$), mais étaient redevenues normales en 4 h. La ventilation/minute et la réponse ventilatoire au dioxyde de carbone étaient significativement déprimées chez tous les patients ($P < 0{,}001$) mais revenaient à des valeurs sub-normales en 4 h. L'anesthésie au fentanyl et à l'Innovar déplaçait la réponse du dioxyde de carbone vers la droite, mais nous n'avons pas trouvé de corrélations entre les valeurs contrôles et l'amplitude du déplacement de la courbe réponse d'une part, et la modification de pente d'autre part. Ceci suggère que les patients qui ont un rapport $\dot{V}\text{I}/P_{CO_2}$ bas ne sont pas plus sensibles à l'action de dépression respiratoire des morphinomimétiques. Le retour à une réactivité respiratoire normale dans les 4 h suivant l'anesthésie se faisait de façon graduelle et progressive. Il n'y avait pas d'arguments en faveur d'un schéma biphasique de récupération.

UBERWACHUNG DER ATMUNG NACH FENTANYL- UND INNOVAR-ANÄSTHESIE

ZUSAMMENFASSUNG

Ventilation ($\dot{V}\text{I}$), End-Atemzug-Kohlensäurespannung ($P\text{E}'_{CO_2}$) und gemischtvenöse Kohlensäurespannung ($P\bar{v}_{CO_2}$) sowie die Reaction der Atemtätigkeit auf CO_2 wurden vor der Operation und während der ersten 4 Stunden der Aufwachphase bei 18 erwachsenen Patienten gemessen, die sich einem elektiven Eingriff an den Extremitäten in Fentanyl- oder Innovar- Narkose unterziehen mussten. Der P_{CO_2} im End-Atemzug volumen und gemischtvenösen Blut nahmen in den ersten 150 min nach der letzten Dosis des Mittels signifikant zu ($P < 0{,}001$, $P < 0{,}01$), kehrten aber nach 4 Stunden zu den Kontrollwerten zurück. Die Ventilation und Reaction der Atemtätigkeit auf CO_2 war bie allen Patienten signifikant unterdrückt ($P < 0{,}001$) normalisierte sich aber in etwa nach 4 Stunden auf die Höhe der Kontrollwerte. Fentanyl-und-Innovar-Narkose verschob die Kohlendioxid-Antwort-Kurve nach rechts, aber weder zwischen der Grösse der Verschiebung noch zwischen der Änderung der Steilheit der Antwort kurve in Verhältnis zu den Kontrollwerten wurde eine Korrelation gefunden. Dies lässt vermuten, dass Patienten mit einem niedrigen Wert von $\dot{V}\text{I}/P_{CO_2}$ nicht stärker anfallig für die Atemdepressive Wirkung von Narkotika sind. Die Erholung der Atemreaction auf normale Ansprechbarkeit während den 4 postoperativen Stunden geschah abgestuft und progressiv; es gab keinen Anhaltspunkt fur einen biphasischen Verlauf der Aufwachphase.

CONTROL DE LA RESPIRACION DESPUES DE LA ANESTESIA CON FENTANILO Y CON INNOVAR

SUMARIO

Se midió la respiración ($\dot{V}\text{I}$), la expiración terminal (P'_{CO_2}), la mezcla venosa ($P\bar{v}_{CO_2}$) y la respuesta ventilatoria al dioxido de carbono durante la operación quirúrjica y durante las cuatro primeras horas de recuperación en 18 adultos que fueron sometidos a intervención quirúrjica electiva de miembros, bajo anestesia de fentanilo o de innovar. La expiración terminal y la mezcla venosa P_{CO_2} aumentaron significativamente a lo largo de los primeros 150 minutos después de la última dosis de droga ($P<0{,}001$, $P<0{,}01$), pero volvieron a los valores de control en el transcurso de 4 horas. La ventilación y la respuesta ventilatoria al dióxido de carbono disminuyeron de forma significativa en todos los pacientes ($P<0{,}001$), pero alcanzaron valores casi iguales a los de control al cabo de las 4 horas. La anestesia con fentanilo e innovar desplazaron la respuesta del dióxido de carbono hacia la derecha, pero no se encontró correlación alguna entre la magnitud del desplazamiento de la curva de respuesta, o la variación del valor de la pendiente, y los valores de control. Esto sugiere que los pacientes con una relación $\dot{V}\text{I}/P_{CO_2}$ baja no son más subsceptibles a la efecto reductor de la ventilacion que producen los narcoticos usados para la anestesia. La recuperación de la respuesta ventilatoria hacia lo normal durante las cuatro horas que siguieron a la operación tuvo lugar de forma gradual y progresiva. No hubo evidencia alguna de una estructura de recuperación de tipo "bifásico".

Br. J. Anaesth. (1982), 54, 605

USE OF MIDAZOLAM AS AN INDUCTION AGENT: COMPARISON WITH THIOPENTONE

S. JENSEN, A. SCHOU-OLESEN AND M. S. HÜTTEL

SUMMARY

A prospective, randomized, single-blind investigation was undertaken into the value of midazolam as an agent for the induction of anaesthesia. Sixty healthy patients undergoing orthopaedic surgery of short duration were allocated randomly to receive either midazolam 0.2 mg kg^{-1} or thiopentone 3 mg kg^{-1}. The induction time (measured as the time until loss of eyelash reflex) in the thiopentone group was significantly shorter than in the midazolam group. No differences were observed between the two drugs as regards time to onset of apnoea, or changes in heart rate and arterial pressure.

Although benzodiazepines have proved useful as alternatives to the barbiturates in the induction of anaesthesia, the use of diazepam has been limited because of its long duration of action (Hillestad et al., 1974); lack of water-solubility (Sarnquist, Mathers and Blaschke, 1979) and the frequency of thrombophlebitis (Olesen and Hüttel, 1980).

Midazolam (Dormicum) (fig. 1) is a new water-soluble benzodiazepine which has been used to induce anaesthesia (Reves et al., 1979). The drug possesses properties similar to those of other benzodiazepines (sedative, anxiolytic, anticonvulsant, muscle-relaxant), and is of low toxicity (Brochure, 1979). Furthermore, it has a short half-life ($T_{\frac{1}{2}} = 1.3-2.2$ h for the beta-phase) (Brochure, 1979) and the frequency thrombophlebitis is low (Jensen, Hüttel and Olesen, 1981; Pagano et al., 1978).

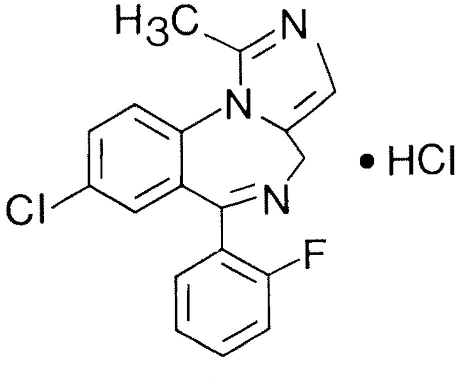

FIG. 1. Structural formula of midazolam.

The present study assessed the value of midazolam as an agent for the induction of anaesthesia and compared its actions with those of an established drug, thiopentone.

PATIENTS AND METHODS

Sixty adult patients (ASA status I–II) admitted to the Departments of Orthopaedic Surgery at Aalborg and Odense hospitals were studied. Each patient was informed of the nature of the study in writing and verbally and consent was obtained from all patients. The study was carried out in accordance with the Helsinki II Declaration. It was a prospective, randomized study and all of the patients were anaesthetized by the authors.

The patients received flunitrazepam 2 mg by mouth as a sedative on the evening before surgery. No premedication was given on the day of surgery. On arrival in the operating theatre cannulae were placed in the left and right cephalic veins. The patients were preoxygenated for 3 min and during this period heart rate, arterial pressure and respiratory frequency were measured. Following the administration of fentanyl 0.05 mg/25 kg body weight via the right cephalic vein, midazolam 0.2 mg kg^{-1} or thiopentone 3 mg kg^{-1} was injected into the left cephalic vein over 30 s. If the eyelash reflex was still present 2 min after this first injection, one-third of the original dose was administered over 30 s at 2 min intervals until the eyelash reflex was abolished. A myoneural blocking drug was administered, the trachea intubated and anaesthesia continued with 0.5% halothane.

Heart rate and arterial pressure (Riva Rocci) were

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TABLE I. *Demographic data of patients (mean ± SD). There is no significant difference in any category*

Group	n	Male/Female	Age (yr)	Wt (kg)	Duration of anaesthesia (min)	Induction dose (mg)
Midazolam	30	20/10	36 ± 12.2	72 ± 9.2	65 ± 20.6	14 ± 1.9
Thiopentone	30	21/9	35 ± 11.8	71 ± 10.9	63 ± 20.1	215 ± 34.3

recorded 1, 2 and 3 min after induction, at 5-min intervals throughout the anaesthetic and 60 min after cessation of anaesthesia. The e.c.g. was monitored throughout the anaesthetic.

At induction, the times to spontaneous closure of the eye, loss of the eyelash reflex, and the onset of apnoea were recorded.

The Mann–Whitney Rank Sum test was used to assess the comparability of the groups. Bartlett's test was used to assess variance homogenicity. To analyse the data, parametric analysis of variance, χ^2-test and Student's *t* test were used.

RESULTS

There were 30 patients in each group and no significant differences as regards sex, age, weight and duration of anaesthesia were demonstrated between the groups (table I). No patient was excluded from the study. The mean dose of midazolam was 14 mg (range 11–18.5 mg) and of thiopentone 215 mg (range 150–300 mg) (table II). Seven patients in the midazolam group and five in the thiopentone group did *not* become apnoeic (this difference was not significant). Baseline cardiovascular indices were similar in the two groups (table III). Immediately before the administration of midazolam mean (± SEM) systolic arterial pressure was 118.5 ± 17.1 mm Hg (diastolic pressure was 70.0 ± 11.5 mm Hg). The lowest arterial pressures were obtained 2 min after the injection: systolic 106.8 ± 15.6 mm Hg and diastolic 63.3 ± 9.5 mm Hg. Immediately before the administration of thiopentone mean systolic arterial pressure was 117.8 ± 17.7 mm Hg. Diastolic pressure was 71.7 ± 9.8 mm Hg. The lowest systolic and diastolic pressures, obtained 2 min after injection, were 106.7 ± 10.1 mm Hg and 69.1 ± 7.9 mm Hg respectively.

Mean (± SEM) heart rate in the midazolam group was 70.9 ± 9.6 beat min^{-1} before induction and this increased to 77.4 ± 11.4 beat min^{-1} 3 min after the administration of the drug.

Baseline mean (± SEM) heart rate in the thiopentone group was 69.0 ± 11.0 beat min^{-1} which inincreased 3 min after injection to 75.7 ± 11.6 beat min^{-1}.

DISCUSSION

In this study the mean induction time was significantly shorter with thiopentone than with midazolam and is in agreement with similar studies by Reves and colleagues (1979) and Fragen, Gahl and Caldwell (1978). With an induction dose of midazolam 0.2 mg kg^{-1} we obtained a mean induction time of 78 s. Reves and co-workers (1979) used the same induction dose and obtained a mean induction time of 73 s, whereas Fragen, Gahl and Galdwell (1978) using 0.15 mg kg^{-1} obtained a value of 175 s.

When we consider the response of the patient to the dose of either drug, assessed on the basis of the standard deviation in the duration of induction, the variation between patients was smaller in the midazolam group than in the thiopentone group. This contrasts with the results obtained by Reves

TABLE II. *Induction data (mean ± SD, range in parentheses)*

	Spontaneous closing of eyes (s)	Disappearance of eyelash reflex (s)	Time to apnoea (s)
Midazolam	57 ± 11.7 (20–65)	78 ± 15.3 (50–110)	71 ± 18.6 (40–120)
Thiopentone	42 ± 10.7 (20–65)	61 ± 20.8 (25–130)	50 ± 15.3 (25–80)
P	< 0.001	< 0.001	< 0.001

TABLE III. *Mean difference between thiopentone and midazolam and 95% confidence limits for difference*

	Mean difference	95% Confidence limits
Systolic arterial pressure (mm Hg)	+3.0	−2.0 and +8.2
Diastolic arterial pressure (mm Hg)	+2.6	−0.8 and +6.0
Heart rate (beat min^{-1})	−2.0	−6.5 and +2.6

and colleagues (1979) who found a considerably greater variation in patients receiving midazolam. The reason for this might be that, besides midazolam or thiopentone, the patients in our study received fentanyl i.v. at induction and it is likely that this could potentiate the effects of midazolam.

Apnoea occurs frequently in thiopentone-induced anaesthesia (Fragen, Gahl and Caldwell, 1978). However, in the present study, no significant difference was observed in the frequency of apnoea between the two drugs (77% in the midazolam group and 83% in the thiopentone group).

No arrhythmias were observed in either group. The fact that no significant differences were found in systolic arterial pressure, diastolic arterial pressure and heart rate between the two drugs, agrees with a similar study by Fragen, Gahl and Caldwell (1978).

ACKNOWLEDGEMENT

Midazolam (Dormicum) was kindly supplied by F. Hoffmann-La Roche.

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ETUDE CLINIQUE SUR LES POSSIBILITES D'UTILISATION DU MIDAZOLAM COMME AGENT D'INDUCTION A LA PLACE DU THIOPENTAL

RESUME

Une étude prospective randomisée en simple aveugle a été entreprise pour préciser la valeur du midazolam comme agent d'induction de l'anesthésie. Soixante sujets en bonne santé subissant des actes brefs de chirurgie orthopédique ont reçu au hasard soit 0,2 mg kg^{-1} de midazolam, soit 3 mg kg^{-1} de thiopental. Le temps d'induction (mesuré comme délai de perte du réflexe palpébral) était significativement plus bref dans le groupe thiopental que dans le groupe midazolam. Les deux agents n'ont pas pu être départagés pour ce qui est du délai de survenue d'une apnée, des modifications de la fréquence cardiaque et de la pression artérielle.

KLINISCHE UNTERSUCHUNG ÜBER DIE ANWENDBARKEIT VON DORMICUM (MIDAZOLAM) ZUR EINLEITUNG IN VERGLEICH ZU LEOPENTAL (THIOPENTAL)

ZUSAMMENFASSUNG

In einer prospektiven, randomisierten Einfach-Blind-Untersuchung wurde über den Wert von Midazolam als Einleitungsmittel für Narkosen befunden. Sechzig Patienten gesunde, die sich einen kurzen orthopädischen Eingriff unterziehen mußten, wurden nach Randomisierung entweder für Midazolam 0,2 mg kg^{-1} oder für Thiopental 3 mg kg^{-1} eingeteilt. Die Einleitungszeit (gemessen als Zeit bis zum Erlöschen des Lindreflexes) war in der Thiopental Gruppe signifikant kürzer als in der Midazolam Gruppe. Hinsichtlich Atemstillstand, Änderungen der Pulsfrequenz und arteriellem Blutdruck sind keine Unterschiede zwischen den beiden Pharmaka beobachtet worden.

USO DEL MIDAZOLAM COMO AGENTE DE INDUCCION: COMPARACION CON LA TIOPENTONA

SUMARIO

Se emprendió una investigación simple-ciega al azar de prospección para establecer el valor del midazolam como agente de inducción de la anestesia. Sesenta pacientes sanos estaban por someterse a operaciones quirúrgicas ortopédicas de corte duración y se les administró al azar ya sea 0,2 mg kg^{-1} de midazolam ya sea 3 mg kg^{-1} de tiopentona. El tiempo de inducción (medido como tiempo transcurrido hasta la pérdida del reflejo de pestaño) en el grupo con tiopentona fue significativamente más corto que en el grupo con midazolam. No se observó ninguna diferencia entre las dos substancias en cuanto al tiempo de aparición de la apnea, ni tampoco hubo cambios en el ritmo cárdiaco y la presión arterial.

Br. J. Anaesth. (1982), 54, 609

COMPARISON OF THE CEREBRAL FUNCTION MONITOR AND PLASMA CONCENTRATIONS OF THIOPENTONE AND ALPHAXALONE DURING TOTAL I.V. ANAESTHESIA WITH REPEATED BOLUS DOSES OF THIOPENTONE AND ALTHESIN

M. FRANK, T. M. SAVEGE, M. LEIGH, J. GREENWOOD AND J. M. P. HOLLY

SUMMARY

Repeated bolus doses of thiopentone or Althesin were administered to 10 patients every 240 s while cerebral electrical activity was recorded with the Cerebral Function Monitor (CFM). Peripheral venous blood samples were collected at 60 and 225 s after each bolus dose for the measurement of plasma concentrations of the drugs. Significant correlations in the range $r = 0.56-0.96$ ($P = 0.02-0.00001$) between plasma thiopentone or alphaxalone concentrations and the upper and lower edges of the CFM trace were found. For the patients with relatively poor correlations, better correlations were obtained when 60- and 225-s samples were analysed separately.

The methods available to monitor and control a defined depth of anaesthesia are imprecise and controversial. Clinical signs dependent on the loss of specific reflexes and changes in the autonomic nervous system have been used since the advent of anaesthesia (Robson, 1969). Although these changes have been found to be fairly consistent with some of the commonly used inhalation anaesthetic agents, the i.v. agents do not demonstrate a predictable association between depth of anaesthesia and clinical signs. The use of neuromuscular blocking agents further interferes with a reliable assessment of depth of anaesthesia. Therefore, it may prove difficult during total i.v. anaesthesia to maintain a careful balance between too light a level of anaesthesia and possible awareness, and too deep a level with, consequently, a more prolonged recovery of consciousness.

Cerebral depression, whether by drugs or other causes is associated with characteristic changes in cerebral electrical activity (Stockard and Bickford, 1975; Marshall, Longley and Stanton, 1965). The electroencephalogram (e.e.g.) has demonstrated similar changes of cerebral electrical patterns in association with increasing depth of anaesthesia during the administration of different anaesthetic agents (Martin, Faulconer and Bickford, 1959; Sadove, Becka and Gibbs, 1967; Scott and Virden, 1972). Distinctive e.e.g. patterns were described by Prior, Maynard and Brierly (1978) at six clinically defined levels of anaesthesia following different rates of infusion of Althesin in primates, and they demonstrated that each e.e.g. pattern had an equivalent CFM signal. Dubois and colleagues (1978) reported the use of the CFM to monitor depth of anaesthesia in man. This was further investigated in a preliminary study which related the plasma concentrations of alphaxalone with the CFM signal during minimal anaesthesia produced by a continuous infusion of Althesin (Savege, Zych and Dubois, 1978).

In the present investigation regular, repeated bolus doses of i.v. anaesthetic agents were administered to provide a rapidly changing pharmacokinetic situation which could be used to test further the relationship between the CFM signal and plasma concentrations of anaesthetic agents.

PATIENTS AND METHODS

Ten healthy patients who had given their informed consent and were undergoing general or gynaecological surgery of moderate duration were included in the study.

Patients were premedicated with papaveretum and hyoscine as experience from preliminary work had shown that unpremedicated patients tended to move during the procedure and the consequent

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disturbance of the electrodes produced artefactual voltages on the CFM. Patients were brought to the anaesthetic room 40 min before the operation was due to start. Biparietal silver/silver chloride electrodes were placed 5 cm apart on either side of the midline, and attached to the CFM (Ormed Ltd) and an awake trace was obtained. Anaesthesia was induced with thiopentone 5 mg kg^{-1} or Althesin 50 μl kg^{-1}, administered over 20 s with a syringe infusion pump. Increments of half the induction dose were injected over 10 s every 240 s following induction. The patients breathed oxygen through a mask and their arterial pressure and heart rate were monitored.

Blood samples for the estimations of drug concentration were taken through a wide-bore indwelling cannula in an antecubital vein of the arm opposite to that used for the injection. Two sets of samples were obtained: one at 60 s after each increment when anaesthesia was judged to be at or near maximum depth; the second at 225 s, that is 15 s before the next bolus, to coincide with the point of maximum recovery from anaesthesia. Three patients also had blood samples collected at 30 s after each bolus. The time and duration of each injection and blood sampling were recorded using the CFM event marker.

Thiopentone concentrations in plasma were determined by gas chromatography based on the micro-method of Flanagan and Withers (1972) and utilizing the nitrogen detector (Breiner and Van Rossum, 1974). The barbiturate was extracted from plasma with chloroform, which was then removed and evaporated to dryness, and the residue redissolved in acetone of which 2 μlitre was injected onto the column. Separation was achieved on a Perkin Elmer Sigma 2 gas chromatograph containing a 2-m glass column packed with GP 3% SP2250 DA on Supelcoport 100–120 mesh (Chromatography Services Ltd) and a carrier gas of nitrogen. Each sample and standard contained an internal standard of propylphenazone which passed through the whole extraction procedure. Plasma alphaxalone concentrations were estimated by a gas chromatographic method. The alphaxalone was extracted from plasma with ether, and a heptafluorobutyrate derivative formed to facilitate separation from endogenous compounds and quantitation by electron capture detection (Exley and Chamberlain, 1967). Separation was performed by gas chromatography on a 2-m column of 5% SE30 coated Gas-Chrom Q. Recovery of alphaxalone throughout the procedure was corrected for by inclusion of an internal standard, 3 β-alphaxalone.

The means of the heights of the upper and lower edges of the CFM trace over the duration of each sampling period were calculated. Correlations between plasma drug concentrations and the upper and lower edges of the CFM trace were calculated using the Statistical Package for Social Sciences, and the significance of the correlations were obtained using table VII of Fisher and Yates.

RESULTS

CFM traces obtained following the regular administration of bolus doses of thiopentone or Althesin tended to show the following characteristics.

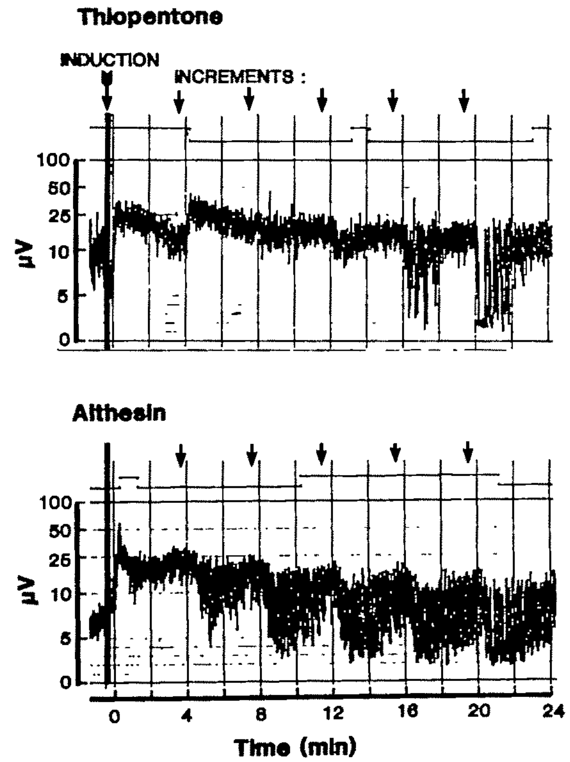

FIG. 1. The upper CFM trace is that of a patient who received regular bolus injections of thiopentone. It shows a peak following induction, and a second peak after the first increment, suggesting the patient was waking up, and anaesthesia was "reinduced". There is a gradual depression of the trace, representing a reduction of cerebral activity following the next two boluses, while the fourth and fifth doses are followed by burst supression activity indicating a much deeper level of anaesthesia; there is a 10-s interval of electrical silence after the fifth dose. The patient's arterial pressure was within normal limits throughout. The lower CFM trace, of a patient who received boluses of Althesin, shows a regular and progressive cerebral depression after each bolus. Burst suppression is reached after the second increment.

Thiopentone. A typical trace obtained with thiopentone (fig. 1) consisted of an initial steep rise from the resting awake trace to a peak within 20–30 s from the beginning of the injection. Usually a second smaller peak occurred after the second bolus of thiopentone. Subsequently, each bolus dose was followed by a gradual depression of the trace. After the fifth injection a more definite and pronounced depression towards the baseline occurred. At this stage, the trace was much broader, ranging from a lower edge of 1–2 μV to an upper edge of 20–25 μV. After the sixth injection, the trace fell abruptly towards the baseline where it remained for 10–12 s before becoming broad again and then rising and narrowing.

When the traces of all the patients who received thiopentone are examined, a similarity in principle of the changes described is evident (fig. 2).

Althesin. The traces obtained from patients receiving Althesin showed a different pattern (fig. 1). The descent from the initial peak following induction was steeper, and was followed by a further marked depression after the second injection. Subsequently, a marked and progressive stepwise descent and broadening of the trace occured after each successive bolus, followed each time by a rise and narrowing of the trace which became less marked as doses accumulated. These changes were generally consistent in all the traces of patients who received Althesin (fig. 3). In figures 4 and 5 (thiopentone and Althesin respectively) the parallel relationships between the CFM and plasma drug concentrations are shown. However, for thiopentone, the first two repeat boluses were followed by further "peaks" after each injection and the opposite relationship between CFM and plasma thiopentone concentration is evident over this period. In table I the correlations between plasma thiopentone or alphaxalone concentrations and the upper and lower edges of the CFM are noted respectively for each patient. (Those measurements following the initial bolus or preceding a second CFM peak after further boluses were excluded.) It is evident that, in general, the lower edge CFM measurements gave a better correlation ($r = -0.75$ to $r = -0.95$) than the upper edge

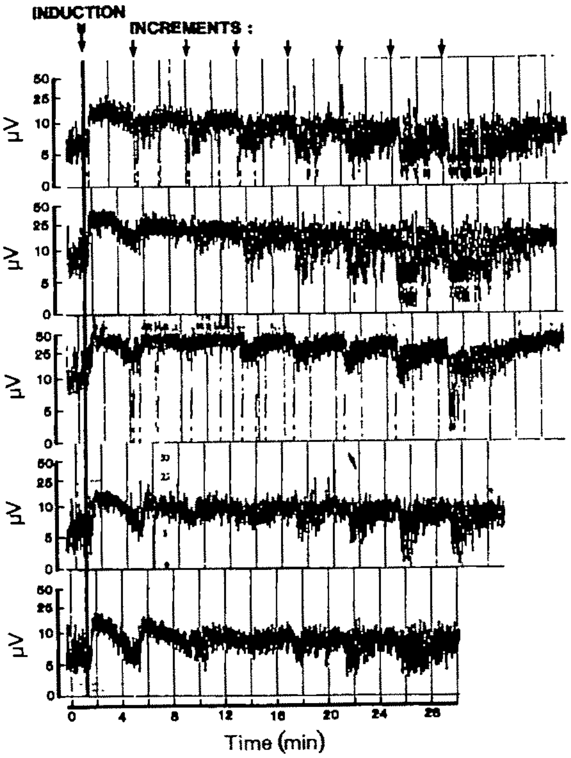

FIG. 2. CFM traces of five patients who received bolus injections of thiopentone.

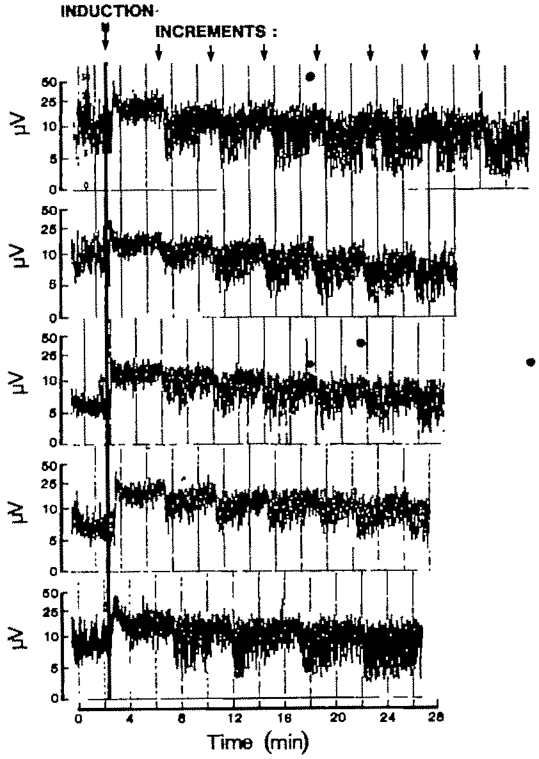

FIG. 3. CFM traces of five patients who received bolus injections of Althesin.

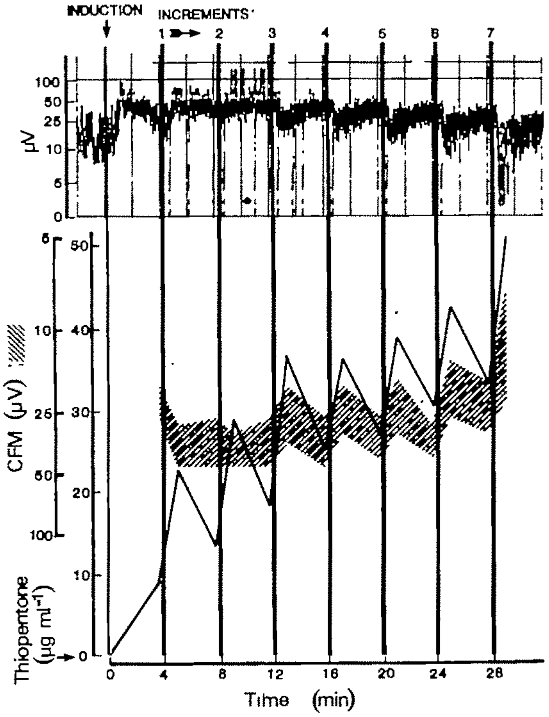

FIG. 4. The CFM trace and plasma thiopentone concentrations of a patient who received equal boluses at regular intervals of thiopentone. The values for the upper and lower edges of the CFM at the time of collection of each blood sample for drug estimation are demonstrated by the shaded area (inverted scale). A parallel trend is evident after the third increment. After the first and second increment, the CFM trace is associated with recovery from, rather than deepening of anaesthesia, as confirmed by the smaller peaks seen after these increments, representing "reinduction" of anaesthesia.

($r = -0.56$ to $r = -0.91$). All correlations are highly significant ($P < 0.02$ on all occasions).

In some patients, for instance patient No. 6 in table I, the correlation and its significance improved markedly when the relationships at 60 s after the bolus and those at 225 s were calculated separately. This is shown graphically in figures 6 and 7 where the plasma thiopentone or alphaxalone concentrations at 60 ("post-incremental") and 225 s ("pre-incremental") have been plotted separately against the upper and lower edges of the CFM for patients Nos 6 and 4 respectively.

The measurements of the plasma drug concentrations for each patient are plotted against the corresponding CFM values in figure 8. Each line represents the best fit curve by the least square error method for the data obtained from one patient.

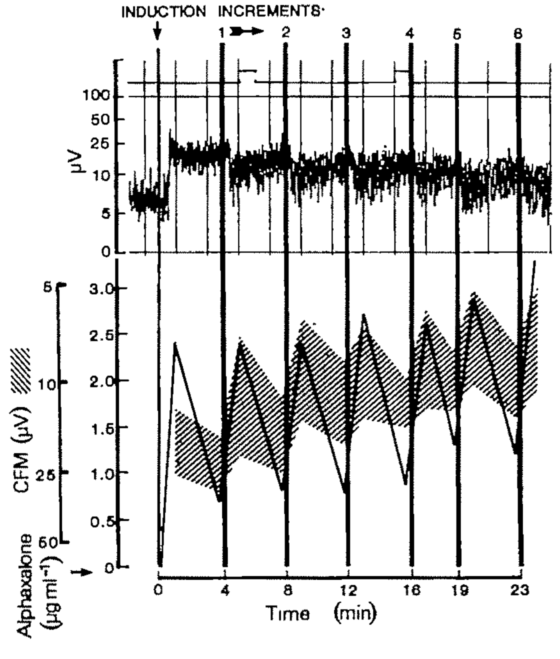

FIG. 5. CFM trace and plasma alphaxalone concentrations of a patient who received equal boluses of Althesin at marked intervals. The heights of the upper and lower edge of the CFM at the time blood samples were collected are demonstrated by the shaded area (inverted scale). A parallel trend is shown from the first increment, suggesting increasing cerebral depression after each bolus.

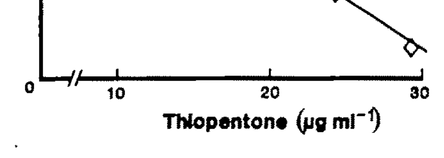

FIG. 6. Relationships between plasma thiopentone concentrations and the upper and lower edges of the CFM trace in patient No. 6. In this case, the thiopentone concentrations 60 s (post-increment) after the bolus injections have a different relationship with the CFM trace, than the values at 225 s (pre-increment).

Although some individual variation is evident, it is notable that there is a clear tendency for the slopes for each drug, and for the upper or lower CFM

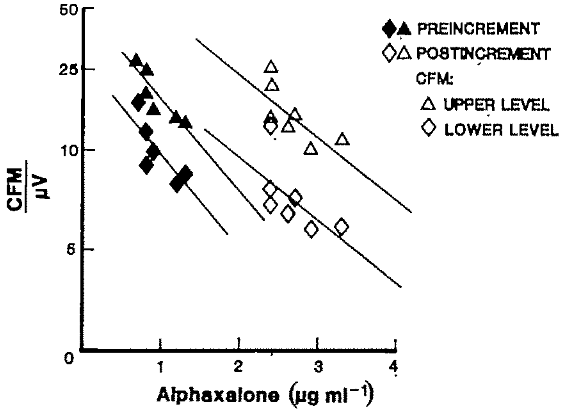

FIG. 7. Relationships between plasma alphaxalone concentrations and the upper and lower edges of the CFM trace in patient No. 4. A separation of the relationships between the 60 (post-increment) and 225- (pre-increment) s samples and the CFM trace, is clearly demonstrated.

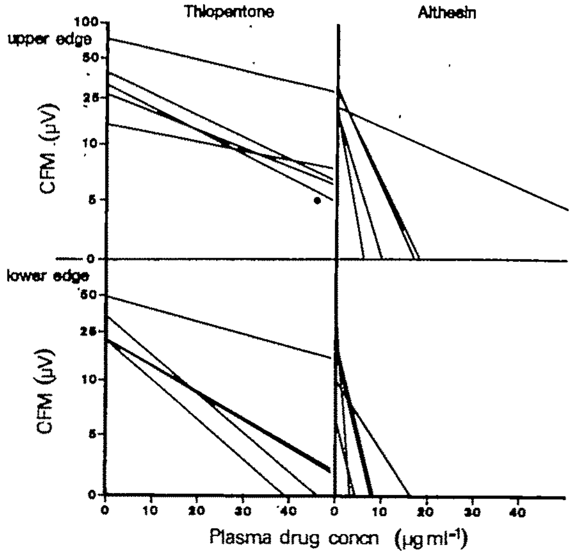

FIG. 8. Relationships between the upper and lower edge of the CFM trace and plasma concentrations of drug of patients who received thiopentone (left) and Althesin (right). The slopes are all negative, indicating reduced CFM traces with increased plasma concentrations. The lower edge relationships are steeper than the upper edge, and a consistent trend is demonstrable with each drug.

TABLE I. *Correlations between the upper and lower edges of the CFM and plasma thiopentone or alphaxalone concentrations which include measurements both at 60 (post-incremental) and 225 (pre-incremental) s following bolus injections. Measurements preceding "preinduction" peaks, (which occurred following the first and sometimes the second repeated thiopentone bolus injection) were excluded, as in this instance the descent of the trace was associated with awakening rather than increasing depth of anaesthesia. Where correlation was less good, as with patient No. 6, the correlation and significance improved markedly when the pre- and post-incremental (PI) relationships were separated, even though the number of observations was halved*

	CFM (mm) – plasma drug concentration					
	Upper edge			Lower edge		
Patient no.	Slope	Correln	*P*	Slope	Correln	*P*
Althesin						
1	−3.19	−0.86	0.01	−11.80	−0.95	0.001
2	−0.42	−0.85	0.01	−1.51	−0.94	0.003
3	−2.09	−0.56	0.02	−3.96	−0.75	0.002
4	−5.79	−0.91	0.00001	−4.51	−0.83	0.0003
5	−1.96	−0.83	0.0002	−4.17	−0.88	0.00003
Thiopentone						
6	−0.17	−0.64	0.02	−0.84	−0.89	0.0002
6PI	−0.39	−0.91	0.005	−1.26	−0.96	0.001
7	−0.46	−0.73	0.001	−0.83	−0.77	0.0006
8	−0.37	−0.76	0.01	−0.57	−0.75	0.01
9	−0.50	−0.82	0.0002	−0.56	−0.81	0.0002
10	−0.22	−0.87	0.0001	−0.26	−0.77	0.002

edges, to cluster together. Three patients who received thiopentone had blood samples taken at 30 s after each bolus injection as well as at 60 and 225 s. There was no correlation between plasma thiopentone concentrations and the CFM trace at 30 s. The plasma thiopentone concentrations of patient No. 10 are shown in figure 9. The 30-s post-incremental plasma concentration was found to rest either on a high peak, or (on two occasions) along the line of the values at 225 s (i.e. "pre-incremental"), while those at 60 and at 225 s showed a consistent trend.

DISCUSSION

The CFM displays cerebral electrical activity as a filtered, integrated and compressed signal. The height of the write-out represents total microvoltage in a semilogarithmic scale, that is the scale is linear up to 12–15 μV, above this value it becomes logarithmic; this exaggerates the changes which take place at low amplitudes when cerebral depression becomes marked. The breadth of the trace corresponds to the difference between maximum and minimum voltages in unit time, that is the variability of cerebral electrical activity.

In anaesthesia, a typical pattern emerges. Following induction, the initial peak from the resting awake trace is consistent with the increased cerebral activity that is associated with induction and light levels of anaesthesia. The descent of the trace following this initial peak is the only ambiguous sign, as it may represent either a deepening of the level of anaesthesia as cerebral activity becomes slower and more depressed, or a lightening of anaesthesia back towards the awake trace. If the latter occurs, the next dose of the drug would be expected to induce another peak of cerebral activity which appears to correspond to reinduction of anaesthesia. This was shown when bolus doses of thiopentone were administered, suggesting a rapid recovery from anaesthesia following the first and sometimes the second injection. In figure 4 the first two boluses after induction were associated with "reinduction" peaks, and the CFM had a reverse relationship to plasma concentrations of thiopentone over this period. The CFM trace obtained with Althesin, in contrast, consistently showed a steep descent, suggesting deepening of anaesthesia following each bolus injection. The subsequent lowering and broadening of the trace, as additional injections of i.v. anaesthetic agent are given, are consistent with further depression of cerebral activity as the drug begins to cumulate and anaesthesia deepens. This is confirmed in figure 5, where a parallel relationship between plasma alphaxalone concentration and CFM is evident from the first bolus on. The alternation between periods of cerebral electrical silence and bursts of activity, that is the e.e.g. "burst suppression" associated with the deeper levels of anaesthesia, is demonstrated in the CFM as a broad band with its lower edge close to the baseline or near electrical silence, and the upper edge representing electrical bursts of activity. The CFM of patients who received thiopentone showed an abrupt onset of burst suppression, usually after the fifth or sixth dose. The CFM of patients receiving Althesin, in contrast, showed a regular and steady increase in depth of anaesthesia, and presumably, cumulation of the drug.

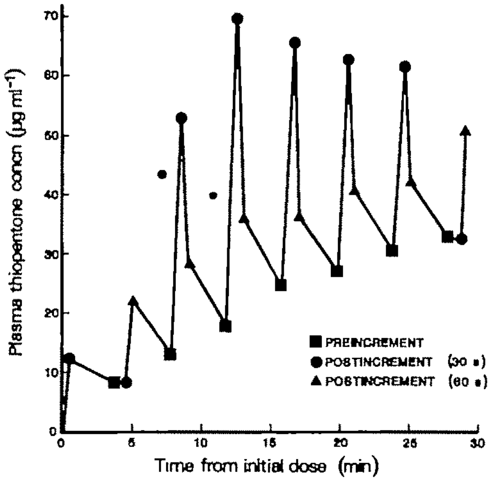

FIG. 9. Plasma thiopentone concentrations of patient No. 10, at 30 s (●) 60 s (▲) and 225 s (■) after each increment. Concentrations at 30 s are variable, some reaching a high value, while two (second and last) lie along the line of pre-incremental values. It is possible that at 30 s the bolus has not mixed properly in the blood compartment.

The preceding description of the CFM output in anaesthesia is in accordance with known changes in cerebral electrical activity during anaesthesia, and the corresponding modification of the signal by the CFM. In the present investigation, the changes in the CFM output during i.v. anaesthesia were further evaluated by comparing them with plasma concentrations of thiopentone or alphaxalone. Plasma concentrations of anaesthetic agents, by virtue of the rapid equilibrium reached with brain concentrations, have been used as a criterion of depth of anaesthesia. However, changing pharmacokinetic and pharmacodynamic effects, variable time lags and other circulatory factors relating to the site of blood sampling, are likely to make plasma drug concentration an insensitive indicator of concurrent cerebral depression.

In some previous studies, a high correlation was found between plasma concentrations of thiopentone and the corresponding brain concentrations or function (Mark et al., 1957; Goldstein and Aronow, 1960; Becker, 1978). However, a lack of correlation between plasma concentrations of thiopentone and cerebral activity or responsiveness was demonstrated by Brand and colleagues (1961) and Dundee and co-workers (1979). These workers suggested the development of acute tolerance as an explanation. In the studies referred to, blood samples for thiopentone estimations were collected from various sites, which included arterial, central venous and peripheral venous.

For the patients used in the present study it was considered unjustifiable to introduce a central venous line, consequently blood was collected from the antecubital vein. The uptake of thiopentone by the tissues in the hand and forearm is not expected to be as avid as that of the brain, and it is likely that this sampling site would give concentrations closer to arterial values (R. E. Bullingham, 1980, personal communication) than those found in blood from the internal jugular vein, where Price (1961) demonstrated that thiopentone concentrations do not reach the initial high peak found in arterial blood. The peripheral venous plasma concentrations shown in figure 9 tend to confirm this. In a recent unpublished study Major, Savege and Verniquet found that plasma diisopropyl-phenol concentrations measured simultaneously in arterial, peripheral venous, and central venous blood, following an initial bolus injection in four patients, showed a changing relationship over the first 60 s following the end of the injected bolus. However, the arterial, peripheral and central venous concentrations of diisopropylphenol became identical within a narrow margin of experimental error, after 60 s.

In the present investigation, there was no correlation between the CFM signal and plasma thiopentone concentrations at 30 s following an i.v. bolus injection. It is possible that, at this interval, the circulating bolus has not yet mixed thoroughly in the circulation (fig. 9). However, plasma thiopentone or alphaxalone estimations at 60 s or later following a bolus, correlated well with the CFM. In the rapidly changing pharmacokinetic situation it was found that the best correlations occurred when the drug concentrations were compared with the CFM at a single point in the 240 s cycle (that is at 60 or at 225 s).

The results of this study indicate that the CFM may provide a direct and reliable measure of anaesthetic depth when using i.v. anaesthetic agents. This is relevant at a time when there is interest in total i.v. anaesthesia as a means of avoiding theatre pollution by inhalation anaesthetic gases, and also to provide a more selective control of "balanced anaesthesia". The quantification of cerebral depression by the CFM may also be used to study the behaviour of i.v. anaesthetic agents. In this study the examination and comparison of traces obtained following the incremental administration of thiopentone or Althesin demonstrated differences in the rate and onset of cumulation and in anaesthetic recovery between these two anaesthetic agents. It is suggested that the inter-drug CFM differences noted reflect differences in their relative potencies and in their pharmacokinetics.

ACKNOWLEDGEMENTS

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UNE COMPARAISON ENTRE LA SURVEILLANCE DES FONCTIONS CEREBRALES ET LES CONCENTRATIONS PLASMATIQUES DE PENTOTHAL ET L'ALPHAXALONE AU COURS DE L'ANESTHESIE GENERALE INTRAVEINEUSE AVEC DES INJECTIONS REPETEES DE PENTOTHAL ET D'ALTHESIN

RESUME

Des doses fractionnées répétées de pentothal ou d'Althesin ont été administrées toutes les 240 s à 10 patients dont l'activité électrique cérébrale était enregistrée par le Cerebral Function Monitor (CFM). Des échantillons de sang veineux périphérique ont été recueillis 60 et 225 s après chaque injection directe pour la mesure de la concentration plasmatique des agents. Nous avons retrouvé des corrélations significatives dans la gamme $r = 0,56$ à $r = 0,96$ ($P = 0,02$ à $P = 0,00001$) entre les concentrations plasmatiques de thiopental ou d'alphaxalone et les franges supérieures et inférieures du tracé du CFM. Pour les patients chez qui les corrélations n'étaient pas très bonnes, on pouvait les améliorer en analysant séparément les échantillons pris à 60 et à 225 s.

EIN VERGLEICH VON EEG-AUFZEICHNUNG UND PLASMAKONZENTRATIONEN VON THIOPENTAL UND ALPHAXALONE WÄHREND INTRAVENÖSER VOLLNARKOSE MIT WIEDERHOLTEN BOLUSINJEKTIONEN VON THIOPENTAL UND ALTHESIN

ZUSAMMENFASSUNG

Wiederholte Bolusinjektionen von Thiopental oder Althesin wurden 10 Patienten alle 240 s verabreicht und das EEG aufgezeichnet. Venöse Blutproben wurden 60 und 225 s nach jeder Bolusdosis zur Messung der Plasmakonzentrationen der Medikamente entnommen. Es ergaben sich signifikante Korrelationen von ungefähr r:0,56 zu r:0,96 ($P < 0,02$ zu $P < 0,00001$) zwischen Plasma-Thiopental oder -Alphaxalone-Konzentrationen und den Höhen und Tiefen der EEG Wellen. Bei den Patienten, die relativ niedrige Korrelation zeigten, erhielt bessere Korrelationen wenn man die Blutproben die nach 60 und 225 s entnommen wurden, getrennt untersucht.

COMPARACION DEL VERIFICADOR DE FUNCION CEREBRAL Y DE CONCENTRACIONES DE TIOPENTONA Y ALFAXALONA DURANTE LA ANESTESIA TOTAL I.V. CON DOSIS REPETIDAS DE BOLO DE TIOPENTONA Y ALTESINA

SUMARIO

Feuron administradas a 10 pacientes cada 240 s dosis de bolo repetidas de tiopentona o de Altesina mientras se registraba la actividad eléctrica cerebral con un Verificador de Función Cerebral (CFM). Se recogieron muestras de sangre venosa periférica a los 60 y 225 s después de cada dosis de bolo para medir las concentraciones de las substancias en el plasma. Se descubrió correlaciones significativas del orden de $r = 0,56-0,96$ ($P = 0,02 - 0,0001$) entre las concentraciones de tiopentona o de alfaxalona y las margénes inferiores y supériores de la señal del CFM. Se obtuvieron mejores correlaciones para los pacientes con correlaciones bastante pobres cuando se analizó las muestras de 60 y 225 s por separado.

Br. J. Anaesth. (1982), 54, 617

EFFECT OF A NEW ANALEPTIC DRUG, ALMITRINE, ON FENTANYL-INDUCED RESPIRATORY DEPRESSION AND ANALGESIA IN MAN

J. H. GAUDY, C. DAUTHIER AND B. FOURGEAUX

SUMMARY

Five female patients received fentanyl 0.0066 mg kg^{-1} i.v. (group A); five other female patients received the same dose of fentanyl, followed immediately by almitrine 0.5 mg kg^{-1} i.v. (group B) and 20 minor gynaecological operations were performed under a combination of almitrine 0.5 mg kg^{-1} and fentanyl 0.0066 mg kg^{-1} (group C). In group A, fentanyl produced a marked and significant respiratory depression ($P < 0.001$). In group B and C, almitrine antagonized the fentanyl-induced respiratory depression. Analgesia did not seem to be affected.

Opiates and opioid drugs are used widely during anaesthesia and after operation for the relief of pain. The major disadvantage of such drugs is respiratory depression and, unfortunately, this side-effect cannot be dissociated from their analgesic activity. If such narcotic-induced depression of ventilation could be antagonized without affecting the analgesia, this would be of value in clinical practice. Naloxone is a specific opiate antagonist which is capable of reversing the ventilatory depressant effect, but it also antagonizes much of the analgesia. Furthermore, a rebound action has been reported (Dauthier, Gaudy and Willer, 1980). At the present time, doxapram hydrochloride seems to be the only analeptic agent which can antagonize, to some degree, the depression of ventilation induced by narcotics, without reversing the analgesic effect significantly (Gairola, Gupta and Pandley, 1980).

Almitrine (bis- (allylamino)-4,6 {(bis (fluoro-4-phenyl) methyl-4-piperazinyl} 2 triazine, bis-methane sulfonate), is a new respiratory stimulant, recently developed in France. Its stimulant action on respiration was established in animals (rat, rabbit, cat and dog) (Laubie and Diot, 1972). In these species, the administration of almitrine 0.1–3 mg kg^{-1} i.v. induced an immediate stimulation of ventilation even at the lowest dose (0.1 mg/kg body weight). The effect of the drug was still noticeable 45 min after administration. In man a dose of almitrine 0.5 mg kg^{-1} i.v. over 20–60 s induced, within a few seconds, hyperventilation which persisted for more than 1 h (Bromet, 1980). In patients with chronic obstructive pulmonary disease (COPD), the effects of 3 mg kg^{-1} by mouth were noticeable within 30 min and lasted for up to 15 h (Bromet, 1980).

Almitrine stimulates the arterial chemoreceptors located at the arch of the aorta and the carotid bodies; the drug does not seem to have any central respiratory stimulant action (Laubie and Diot, 1972). This characteristic may explain the lack of cortical stimulation and the absence of convulsions. Almitrine has been recommended for treating patients with COPD (Neukirch et al., 1974; Schrijen and Romero-Colomer, 1978; Sergysels et al., 1978) and recent studies have confirmed that, besides its action as a respiratory stimulant, almitrine is able to modify pulmonary shunting (du Cailar et al., 1980).

In 1972, Courtois and colleagues demonstrated that, in the rat and rabbit, almitrine antagonized the depressant effects induced by morphine, without affecting the analgesia. In the anaesthetized dog, fentanyl-induced ventilatory depression was inhibited by almitrine, with only minimal changes in the analgesic effect (Dauthier, Gaudy and Willer, 1980). The scope of the present study was to investigate evidence of its effectiveness in man. Two series of investigations have been carried out: first, the potency of almitrine as an antagonist of fentanyl-induced ventilatory depression was determined and second, the effects of almitrine, when used in association with fentanyl in minor surgical operations, were delineated with a particular regard to adequacy of ventilation and analgesia.

PATIENTS AND METHODS

The study was carried out on young healthy female

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patients (20–30 yr) who were selected from a series of patients admitted either for termination of pregnancy (TOP) or for minor gynaecological procedures. Explanations were given as to the purpose and procedure, and 30 patients were chosen with their consent. A preliminary assessment based on clinical history, physical examination, routine chest radiograph and e.c.g., was performed and established that the patients were free from cardiopulmonary disease. No premedicant was administered before anaesthesia. A forearm vein was cannulated and a solution of 5% dextrose infused slowly.

Initially, the ventilatory effects of fentanyl alone were studied and then those produced by the combination of fentanyl and almitrine. Five patients received fentanyl 0.0066 mg kg^{-1} i.v. in 20 s (group A). Five other patients received the same dose of fentanyl, immediately followed by almitrine 0.5 mg kg^{-1} i.v. in approximately 60 s (group B). Ventilation was measured using a Fleisch pneumotachograph (No. 2) fitted with a plastic transparent mask in the 5 min preceding, during and immediately after the administration of the drug(s). The mask was carefully adjusted on the face of the patient, who was allowed to breathe room air. Before and after each study the pneumotachograph was calibrated with a 646-ml syringe.

The resulting spirogram (flow rate and integrated tidal volume) was displayed on a polygraph. The tidal volume (*V*T) and the respiratory frequency (*f*) were measured and the minute ventilation (*V*E) calculated as follows: $V_E = V_T \times f$. E.c.g. (lead II) was continuously recorded and displayed on an oscillograph. Arterial pressure was measured at 2-min intervals by means of a sphygmomanometer.

In a subsequent part of the investigation the effects of almitrine in association with fentanyl were studied. Twenty patients admitted for TOP (suction curettage) (group C) were included. Almitrine 0.5 mg kg^{-1} was administered i.v. in approximately 1 min. Within 1 min of this first injection, when the first evidence of ventilatory stimulation appeared (essentially tachypnoea), fentanyl 0.0066 mg kg^{-1} was injected in 20 s. The surgical procedure started within the subsequent 2 min. In the 5 min preceding, during and for the 10 min following the administration of the drugs (i.e. the average duration of the surgical procedure) $F_{E'}\mathrm{CO_2}$ (Gould-Godart capnograph) and $S\mathrm{aO_2}$ (Hewlett–Packard oximeter) were measured continuously. (Owing to unexpected circumstances, the capnograph and oximeter were not available simultaneously, and it was not possible to estimate the pulmonary ventilation by comparing the results obtained from the readings on the pneumotachograph and those expressed by using $F_{E'}\mathrm{CO_2}$ and $S\mathrm{aO_2}$.) Arterial pressure was measured by means of a sphygmomanometer, before the first injection, within 1 min of the first injection, and at 5-min intervals thereafter. All patients were observed closely for 1 h after the end of the operation. Paired Student's *t* test was used to assess statistical probability.

RESULTS

Ventilatory effects induced by fentanyl (group A) and by the combination of almitrine and fentanyl (group B)

Group A (fig. 1). Fentanyl 0.0066 mg kg^{-1} i.v. induced marked hypoventilation. In the interval between the 1st and the 2nd min after the injection, ventilation (*V*E) decreased significantly ($P < 0.001$), with decreases in both *V*T ($P < 0.001$) and *f* ($P < 0.02$).

Bradypnoea occurred immediately after the 2nd min, and necessitated discontinuation of any further measurements. At this stage the patients were given oxygen and oral encouragement to stimulate ventilation. Thereafter, anaesthesia was induced in a routine manner.

The only side-effects that occurred were a sensa-

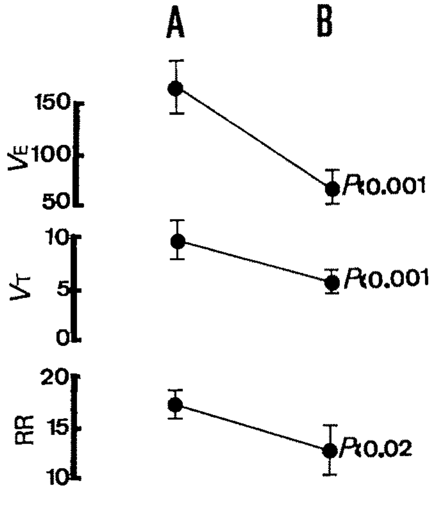

FIG. 1. Group A. Ventilatory effects of fentanyl 0.0066 mg kg^{-1} i.v. A: before the injection; B: at about 1–2 min after the injection. *V*E = expired volume per minute (ml kg^{-1}); *V*T = tidal volume (ml kg^{-1}); RR = respiratory rate per minute. *V*E, *V*T, *f* are mean value ± SD.

tion of itch and of warmth, predominantly on the face and the antero-superior part of the chest. A moderate bradycardia was noted also and could be prevented by atropine 0.25 mg i.v.

Group B (fig. 2). Almitrine 0.5 mg kg^{-1}, administered after fentanyl 0.0066 mg kg^{-1} inhibited the hypoventilation. Decreases in $\dot{V}$E, $\dot{V}$T and f were small but significant. Five patients complained of pruritus and two of nausea. The injection of fentanyl induced a slight bradycardia, which disappeared after the administration of almitrine. The patients were observed for 5 min, before anaesthesia was induced as in group A.

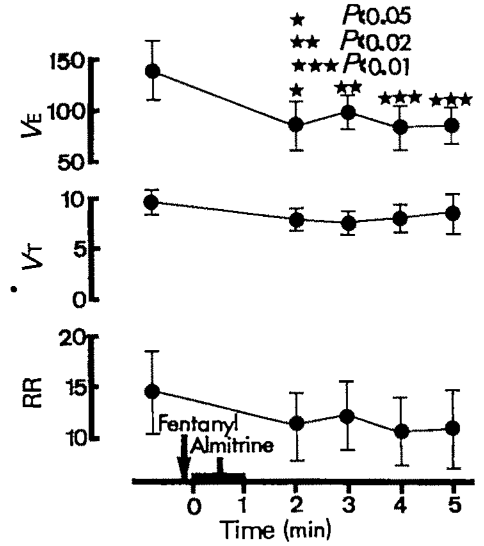

FIG. 2. Group B. Ventilatory effects of the combination of fentanyl 0.0066 mg kg^{-1} and almitrine 0.5 mg kg^{-1}. $\dot{V}$E = expired volume per minute (ml kg^{-1}); $\dot{V}$T = tidal volume (ml kg^{-1}); RR = respiratory rate per minute. $\dot{V}$E, $\dot{V}$T, f are mean value ± SD.

Ventilatory and analgesic effects of a combination of almitrine and fentanyl in minor gynaecological operations

Group C (fig. 3). The combination of almitrine and fentanyl was used in 20 patients undergoing suction termination of pregnancy. The average duration of the surgical procedure did not exceed 10 min. One minute after the administration of almitrine hyperventilation was observed, leading to a decrease in FE'CO_2 and a slight tachycardia. After the administration of fentanyl, and during the 10 min required for the surgical procedure, FE'CO_2 and SaO_2 showed no significant variations, and the heart rate returned to normal. The major side-effects were pruritus and, in some patients, nausea.

The gynaecological operations were carried out as usual, although operation conditions were not ideal. In the 1 h following the operation, there were no changes in respiratory rate or arterial pressure. The patients remained sleepy for less than 2 h after the operation. Nevertheless, during this period they could be easily roused and were able to speak, cough and swallow. Although they had no recall of anaesthesia or surgery, some of the patients had dreams (five patients) and others nightmares (two patients).

DISCUSSION

Opioid drugs are used widely during anaesthesia and for the relief of pain after operation.

At the present time, newer and more potent analgesic drugs, such as fentanyl, have superseded the more conventional analgesic drugs, such as pethidine. Morphine is still frequently used, particularly in cardio-thoracic surgery and for the relief of pain. All these drugs are potent respiratory depressants and, unfortunately, analgesia and respiratory depression seem to be linked closely. Furthermore, the respiratory depression induced by opiates is potentiated by the anaesthetic drugs, including nitrous oxide, and numerous other drugs such as tranquillizers and neuroleptic agents. Respiratory depression occurring during the surgical operation can be managed by artificial ventilation. Respiratory depression in the period following surgery is a greater problem.

Many analeptic drugs have been used in an attempt to overcome this problem. The conventional analeptic drugs (strychnine, picrotoxin, pentylenetetrazol) are no longer used on account of their

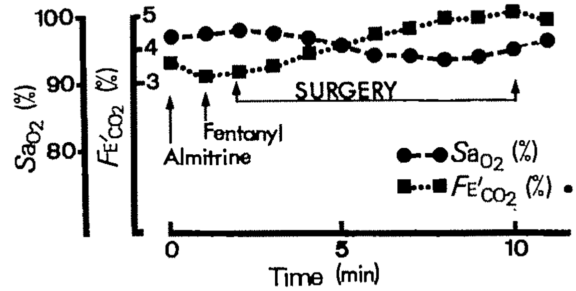

FIG. 3. Group C. Arterial oxygen saturation (SaO_2 = mean value) and carbon dioxide fractional concentration in end-expiratory gas (FE'CO_2 = mean value) after the administration of almitrine 0.5 mg kg^{-1} plus fentanyl 0.0066 mg kg^{-1} in 20 patients scheduled for TOP.

side-effects. They act mainly as central nervous system stimulants, thus inducing restlessness, disorientation, euphoria, optical hallucinations, dizziness, sweating, pyrexia, headache and convulsions and in very high doses, hypotension (Wang and Ward, 1981). Doxapram is used frequently. Although it has been demonstrated that doxapram could prevent narcotic-induced hypoventilation, without impairing the analgesic effect (Gupta and Dundee, 1974a, b; Gairola, Gupta and Pandley, 1980), side-effects have been reported: prolonged pressor effect, tachycardia, extrasystoles, irregular heart rhythm (Wang and Ward, 1981).

Almitrine is a new analeptic drug which acts via the arterial chemoreceptors in the arch of the aorta and the carotid bodies. In animals (rat, rabbit, dog) the ventilatory depression induced by morphine or fentanyl was inhibited by almitrine without causing any major change in analgesia. The present study demonstrates the efficacy of almitrine in man as an antagonist to the respiratory depressant effect of fentanyl. In group A, fentanyl produced a marked decrease in ventilation. Almitrine 0.5 mg kg^{-1} inhibit this respiratory depression. In addition, in group C, there was no evidence of respiratory depression either during operation or during the first hour following anaesthesia.

In group C, the efficacy of analgesia was more difficult to assess than the effects on ventilation. It should be emphasized that these surgical procedures carried out after the administration of almitrine in association with fentanyl were practically painless. While undergoing surgery none of the patients complained of pain or discomfort. Indeed, they all declared afterwards that they had no recollection of any pain. However, as tactile sensibility and hearing were unimpaired, the patients sometimes made involuntary muscle movements and these unwanted effects posed difficulties for the surgeon. Indeed, only an objective technique for the evaluation of pain might give a complete explanation of the mechanism of analgesia and whether pain relief was complete.

The dissociation between ventilation and analgesia is difficult to explain. Opiate iontophoresis on respiratory related units (RRU) (Denavit-Saubie, Champagnat and Zieglgänsberger, 1978) or in the periaqueductal grey matter (Gent and Wolstencroft, 1976a, b) excites some neurons while inhibiting others.

Consequently, the lowering of spontaneous or induced firing of RRUs is related closely to the ventilatory effects produced by the opiates. Fentanyl acts on respiratory cells by impairing the transmitted synaptic impulse. The firing discharge is depressed selectively during the maximal frequency (inspiration) without impairing expiration (Denavit-Saubie, Champagnat and Zieglgänsberger, 1978). Therefore almitrine may be capable of obtunding this effect without altering the mechanism of analgesia.

Although the results of the present study show that, in man, almitrine will antagonize respiratory depression induced by a morphinomimetic analgesic without abolishing the analgesic effect, a number of points deserve consideration. Since almitrine acts on peripheral arterial chemoreceptors, its action may be modified by certain anaesthetics, in particular those drugs that modify the response of these receptors to hypoxia (Weiskopf, Raymond and Severinghaus, 1974; Hirschman et al., 1975; 1977). The action of almitrine may also be modified by increasing oxygen concentrations (Guillerm and Radziszewski, 1974).

Since the threshold of clinical activity corresponds to a plasma concentration of 100 ng ml^{-1}, and since direct i.v. injection leads to greater plasma concentrations, infusion is the best route during the early period after operation (Bromet, 1980). Oral administration also produces adequate plasma concentrations, and might prove advantageous in the period after operation. The use of almitrine together with fentanyl, even for minor surgical procedures, is probably of a limited interest because of the possible side-effects and the poor operating conditions.

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EFFET D'UN NOUVEL AGENT ANALEPTIQUE, L'ALMITRINE, SUR LA DEPRESSION RESPIRATOIRE ET L'ANALGESIE INDUITES PAR LE FENTANYL CHEZ L'HOMME

RESUME

Cinq patientes ont reçu 0,0066 mg kg^{-1} de fentanyl i.v. (groupe A); cinq autres patientes ont reçu la même dose de fentanyl immédiatement suivie de 0,5 mg kg^{-1} d'almitrine i.v. (groupe B); et 20 actes de chirurgie gynécologique mineure ont été effectués avec l'association d'almitrine 0,5 mg kg^{-1}, et de fentanyl 0,0066 mg kg^{-1} (groupe C). Dans le groupe A, le fentanyl a entraîné une dépression respiratoire marquée et significative ($P < 0{,}001$). Dans les groupes B et C, l'almitrine a antagonisé la dépression respiratoire induite par le fentanyl. L'analgésie n'a pas semblé en être affectée.

DIE WIRKUNG EINES NEUEN ANALEPTIKUMS, ALMITRIN AUF DIE DURCH FENTANYL HERVORGERUFENE ATEMDEPRESSION UND ANALGESIE BEIM MENSCHEN

ZUSAMMENFASSUNG

Fünf weibliche Patienten erhielten Fentanyl 0,0066 mg kg^{-1} i.v. (Gruppe A); fünf weitere weibliche Patienten erhielten die selbe Dosis von Fentanyl und sofort darauf Almitrin 0,5 mg kg^{-1} (Gruppe B); und 20 gynäkologische Kurzeingriffe wurden mit einer Kombination von Fentanyl und Almitrin durchgeführt (Gruppe C). In Gruppe A rief Fentanyl eine deutliche und signifikante Atemdepression hervor ($P < 0{,}001$). In Gruppe B and C hob Almitrin die durch Fentanyl hervorgerufene Atemdepression auf. Die Analgesie schien nicht beeinflusst zu werden.

EFECTO DE UNA NUEVA SUBSTANCIA ANALEPTICA, ALMITRINA, SOBRE LA ANALGESIA Y LA DEPRESION RESPIRATORIA INDUCIDAS POR FENTANILO

SUMARIO

Cinco pacientes mujeres recibieron 0,0066 mg kg^{-1} de fentanilo i.v. (Grupo A); cinco pacientes mujeres más recibieron la misma dosis de fentanilo, seguida de inmediato por 0,5 mg kg^{-1} de almitrina i.v. (Grupo B) y se llevaron a cabo 20 operaciones ginecológicas menores bajo una combinación de 0,5 mg kg^{-1} de almitrina y 0,0066 mg kg^{-1} de fentanilo (Grupo C). En el Grupo A, el fentanilo produjo una depresión respiratoria significativa y marcada ($P < 0{,}001$). En los Grupos B y C, la almitrina antagonizó la depresión respiratoria inducida por el fentanilo. No pareció ser afectada la analgesia.

Br. J. Anaesth. (1982), **54**, 623

COMPARATIVE STUDY OF LORAZEPAM AND TRIMEPRAZINE FOR ORAL PREMEDICATION IN PAEDIATRIC ANAESTHESIA

C. G. PETERS AND J. T. BRUNTON

SUMMARY

One hundred and ninety-nine children received either lorazepam 0.05 mg kg^{-1} or trimeprazine 3 mg kg^{-1} as oral premedication in a double-blind trial. Lorazepam proved more palatable and produced a cheerful demeanour, but possessed no significant advantages on overall assessment before surgery. Following operation, restlessness with vomiting, and evidence of retrograde amnesia occurred more frequently with lorazepam.

Although certain benzodiazepines produce good anxiolysis in children (Lindgren, Saarnivaara and Himberg, 1980), the use of lorazepam as a premedicant in children has not been investigated despite its widespread use in adults. We have compared lozazepam with trimeprazine, the established drug (Davies and Doughty, 1966), adapting the method of Doughty (1959).

PATIENTS AND METHODS

All children older than 1 year of age admitted for ear, nose and throat (e.n.t.) surgery were assessed before operation for demeanour, and randomly allocated to receive lorazepam 0.05 mg kg^{-1} or trimeprazine 3 mg kg^{-1} as premedication, the doses being derived from a previous pilot study. The hospital pharmacist coded the drugs and prepared nine incremental doses of each from powdered tablets. The powders were rendered indistinguishable. Premedication was given double-blind, according to bodyweight (table I) and administered by mouth with orange syrup B.P. 5 ml 2 h before surgery.

Demeanour, palatability of the mixture, and verbal response or hand withdrawal on venepuncture, were recorded in the anaesthetic room. Anaesthesia was induced with thiopentone 5–6 mg kg^{-1} i.v. Atropine 0.01 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} were administered via a 23- or 25-s.w.g. winged needle, before endotracheal intubation. The children breathed spontaneously a mixture of nitrous oxide, oxygen and 1–2% halothane.

The antisialagogue effect of the drugs and any adverse event at induction were noted. For 4 h after the operation the same recovery and ward nurses recorded heart rate half-hourly and any evidence of vomiting, restlessness or pallor. Any requirement for morphine 0.2 mg kg^{-1} i.m., for the relief of pain, was recorded.

On the first day after the operation, each child was asked by one of the authors if he remembered receiving the premedication and whether it was pleasant. Recall of the injection and any associated pain was noted. The presence of a sore throat was sought. Answers were recorded as yes, no or undecided. The results were analysed using a commercially available standard computer program known as the Statistical Package for the Social Sciences, version 5, incorporating the Chi-squared test with Yates' correction where appropriate.

RESULTS

One hundred and ninety-nine sets of results were completed. Eighty-seven children received trime-

TABLE I. *Premedication dosage regimen*

Premedication powder number	Body weight (kg)	Trimeprazine (mg)	Lorazepam (mg)
1	8–12	30	0.50
2	13–17	45	0.75
3	18–22	60	1.00
4	23–27	75	1.25
5	28–32	90	1.50
6	33–37	105	1.75
7	38–42	120	2.00
8	43–47	135	2.25
9	48–52	150	2.50

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prazine and 112 lorazepam. The two groups were comparable (table II).

Palatability of premedicant

Of the children receiving lorazepam, 75.9% liked the taste whereas only 42.5% of the trimeprazine group responded favourably. Forty-seven per cent expressed distaste for trimeprazine compared with only 21.4% for lorazepam. This preference for lorazepam in orange syrup was statistically significant ($P < 0.01$).

Demeanour

Those children who were comatose, sleepy, serious or cheerful were classified as having a "satisfactory" demeanour and those presenting in tears, apprehensive or unco-operative as "unsatisfactory". Table III shows no difference in satisfactory demeanour between the two groups before or after premedication. However, individual demeanour differed after premedication, there being a greater tendency to be cheerful following lorazepam and to be sleepy after trimeprazine ($P < 0.01$).

Response to venepuncture

Wincing or lack of verbal response and absence of hand withdrawal on venepuncture were considered satisfactory responses, whereas non-co-operation, or crying and withdrawal of the hand, were classified as unsatisfactory. No difference existed in the response to venepuncture. In the trimeprazine group, 81.6%, and in the lorazepam group 81.3% were satisfactory in relation to the verbal response, with 72.4% and 75.9% respectively being satisfactory for the hand withdrawal response.

Overall "satisfactory" behaviour

Children displaying overall satisfactory behaviour were those satisfactory both in demeanour and in response to venepuncture, the remainder being unsatisfactory. Overall satisfactory behaviour was displayed by 56.3% of the trimeprazine group and by 60.7% of those receiving lorazepam, the difference lacking statistical significance. Overall satisfactory behaviour increased with increasing age (fig. 1).

Antisialagogue effect

At laryngoscopy, the antisialagogue effect was considered satisfactory if the pharynx and larynx were dry or moist, but unsatisfactory if wet and requiring suction. Of those receiving trimeprazine 95.4% were satisfactory, as were 89.3% of the lorazepam group. This difference lacked significance.

Adverse events on induction

During induction one child coughed and one suffered transient laryngospasm. Both had received lorazepam.

TABLE II. *Details of patients in the two groups. *Females were allocated the value 1, males the value 2, the means of the accumulated values being compared*

	Mean age		Mean sex*		Mean weight		Premedication to induction time		Duration of operation	
Group	(yr)	SD	(value)	SD	(kg)	SD	(min)	SD	(min)	SD
Trimeprazine	7.59	2.87	1.49	0.50	27.22	10.57	138.70	26.78	22.35	8.12
Lorazepam	7.64	2.70	1.58	0.71	26.10	8.29	138.64	24.70	23.69	10.80
P	0.91		0.32		0.38		0.96		0.32	

TABLE III. *Percentage frequency of demeanour before premedication and before induction*

	Satisfactory demeanour					Unsatisfactory demeanour			
	Comatose	Sleepy	Cheerful	Serious	Overall	Apprehensive	Tearful	Unco-operative	Overall
Before premedication									
Trimeprazine	0	0	62.1	32.2	94.3	3.4	2.3	0	5.7
Lorazepam	0	0	70.5	25.0	95.5	1.0	3.5	0	4.5
Before induction									
Trimeprazine	1.1	28.8	23.0	29.9	82.8	8.0	6.9	2.3	17.2
Lorazepam	0	6.3	57.1	20.5	83.9	8.0	7.1	1.0	16.1

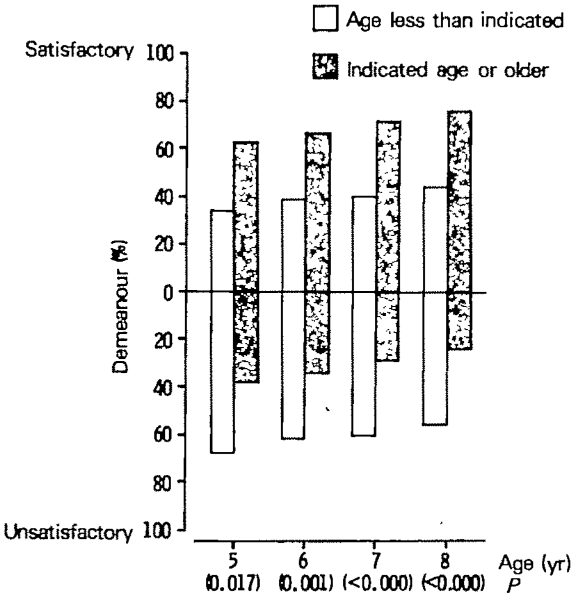

FIG. 1. The combined percentage frequency of satisfactory and unsatisfactory demeanour in the anaesthetic room at differing ages. The significance of the difference in demeanour between those below the indicated age and those of the indicated age and above is given by the *P* value.

Postoperative sequelae

Table IV shows a significant increase in vomiting and restlessness in the period after operation amongst those receiving lorazepam. The frequency of pallor was similar in both groups, as was the need for analgesia. Although lorazepam was associated with a more rapid heart rate in the period after operation, this reached statistical significance only at 90 min (fig. 2) ($P < 0.02$).

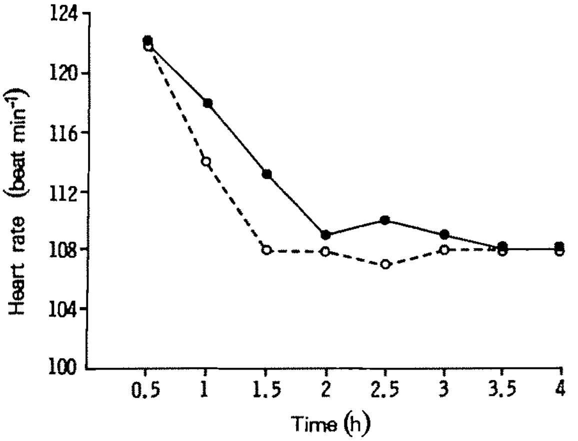

FIG. 2. The mean heart rates of the trimeprazine (○ - - - - ○) and lorazepam (●——●) groups obtained in the period following operation.

TABLE IV. *Percentage frequency of sequelae and need for analgesia in the period after operation*

	Trimeprazine group		Lorazepam group		
	Some	None	Some	None	*P*
Vomiting	11.5	88.5	39.3	60.7	<0.01
Restlessness	49.4	50.6	64.3	35.7	0.03
Pallor	5.7	94.3	6.2	93.8	n.s.
Analgesia	18.4	81.6	18.8	81.2	n.s.

TABLE V. *Percentage results of questioning undertaken, following operation*

	Trimeprazine	Lorazepam	*P*
Recall of receiving premedication			
Yes	89.7	90.1	
No	9.2	8.9	n.s.
Undecided	1.1	0.8	
Recall of venepuncture			
Yes	86.2	79.4	
No	9.2	19.6	0.03
Undecided	4.6	0.9	
Palatability of premedication			
Yes	33.4	55.4	
No	58.6	34.8	<0.01
Undecided	8.0	9.8	
Pain on venepuncture			
Yes	32.0	24.1	
No	49.4	54.4	n.s.
Undecided	18.3	21.4	
Postoperative sore throat			
Yes	80.4	79.4	
No	17.2	19.6	n.s.
Undecided	2.2	0.9	

Postoperative questioning (table V)

An equally small percentage of each group were unable to recall receiving premedication, but a significantly larger number of children were unable to recall venepuncture after lorazepam, which was again the more palatable premedication. No difference existed between the two groups in appreciation of pain on venepuncture or sore throat.

Other side-effects

Three children who received lorazepam experienced hallucinations. One child was affected 30 min after premedication, but recovered before arriving in the anaesthesia room. The other two children experienced hallucinations following the operation. There were no sequelae and no treatment was required.

DISCUSSION

This study was intended to evaluate the use of lorazepam by mouth in paediatric patients undergoing e.n.t. surgery. Lorazepam possesses the advantage of greater anxiolysis than narcotic premedication (Wassenaar et al., 1977), lack of respiratory depression (Dodson et al., 1976; Cormack, Milledge and Hanning, 1977), anterograde amnesia, long duration of action (Dundee et al., 1977) and an antiemetic effect (Loach and Fisher, 1975).

Lorazepam is absorbed efficiently following both i.m. and oral administration (Diamond, 1978), but is not commercially available in syrup or suspension form because of lack of stability. As powdered tablets, the bitter taste of trimeprazine was not entirely disguised by orange syrup B.P., but the preference for lorazepam persisted into the period after operation.

Children tended to be cheerful after lorazepam and to be sleepy or serious after trimeprazine, but both drugs produced satisfactory demeanour in approximately 83%, equivalent to that of children given only oral atropine (Beeby and Hughes, 1980). These authors, however, used a playroom with a voluntary worker within the theatre suite as a substitute for drug premedication. Lacking these facilities we felt unjustified in including a control group within our trial. Trimeprazine produced the only comatose children in this series, confirming previous reports (Davies and Doughty, 1966).

Our results for satisfactory verbal response, lack of hand withdrawal on venepuncture and overall satisfactory behaviour in the anaesthetic room are similar to those for trimeprazine reported by Davies and Doughty (1966) and lorazepam has demonstrated no significant advantage. We simplified the classification of verbal response by omitting the category "whimpered", which other authors have considered satisfactory.

Our procedure included the induction of anaesthesia by i.v. injection, but in individual anaesthetic practice a gaseous induction may be chosen when appropriate, resulting in satisfactory demeanour on induction in more than 90% of children (Boyd and Manford, 1973; Beeby and Morgan Hughes, 1980).

No significant difference could be demonstrated in satisfactory demeanour between lorazepam and trimeprazine, therefore the combined results were analysed by age. The frequency of satisfactory demeanour increased with increasing age (fig. 1). This confirms a similar observation for trimeprazine by Davies and Doughty (1966). After oral diazepam or flunitrazepam, blood concentrations and anxiolysis were significantly less in those younger than 5 years of age compared with older children, possibly as a result of alterations in gastric pH affecting absorption (Lindgren, Saarnivaara and Himberg, 1980). Conversely, an age-dependent difference in demeanour was not observed in children receiving only oral atropine premedication (Beeby and Morgan Hughes, 1980). It is possible that the inferior response to some premedicant drugs in younger children, including trimeprazine and lorazepam, is the result of age-dependent pharmacokinetics.

Both drugs produced an adequate antisialagogue effect in this series, in contrast to the effect of lorazepam in adults, where excess salivation occurs, particularly in intubated patients (Dodson and Eastley, 1978). The low frequency of pallor after operation in the present series is in contrast to the 68% frequency found by Davies and Doughty (1966) using trimeprazine solution and is not readily explained, although identical criteria were used.

The frequency of vomiting after anaesthesia in the trimeprazine group was similar to that reported after trimeprazine in previous studies. The frequency of postoperative vomiting after premedication with lorazepam was 39.3%, which is greater than the 10.4% (Dodson and Eastley, 1978) and 15% (Dundee et al., 1977) frequency observed in adults. Both groups received equal amounts of analgesic, following surgery, but whereas trimeprazine has a well recognized antiemetic effect, opinion is divided concerning lorazepam, with both antiemetic and emetic properties reported (Dodson et al., 1976). This emetic effect after lorazepam premedication may predominate in children.

In the period after surgery with trimeprazine, 49.4% were considered restless, a frequency which compares favourably with the 90% reported by Davies and Doughty (1966). In the lorazepam group 64.3% were considered restless which was possibly responsible for the increase in heart rate at 1.5h. This is contrary to the effect of lorazepam in adults where restlessness (L'Armand et al., 1980), agitation and hallucinations (Pagano et al., 1978) have been reported to occur before surgery. In the present series hallucinations occurred before surgery in a child prone to nightmares and following operation in another similar child. Hallucinations do not appear to be associated with phenothiazine premedication in children.

The frequency of anterograde amnesia for the venepuncture was less than the 28% rate reported in adults (Dundee et al., 1977). However, amnesia following oral lorazepam is greater for non-emotional or visual events than for painful stimuli (McKay, Dundee and George, 1978; Studd and Eltringham, 1980). We observed no difference in appreciation of pain on venepuncture or postoperative sore throat between the two groups.

CONCLUSION

Although recommended for routine premedication in adults, lorazepam has no advantage over trimeprazine for routine premedication in children before e.n.t. surgery. Its use is associated with a greater frequency of undesirable sequelae which could be disadvantageous with a potentially compromised airway. The method of administering premedication was acceptable to children and nursing staff and may warrant further consideration in view of the inappropriate formulation of some potentially useful drugs.

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ETUDE COMPARATIVE DU LORAZEPAM ET LA TRIMEPAZINE POUR LA PREMEDICATION ORALE EN ANESTHESIE PEDIATRIQUE

RESUME

Dans une étude en double aveugle, 199 enfants ont reçu soit du lorazepam 0,05 mg kg^{-1}, soit de la trimepazine 3 mg kg^{-1}, comme prémédication per-os. Le lorazepam s'est révélé meilleur au goût et entraînant un comportement euphorique, sans qu'il apparaisse d'avantages sigificatifs pour la préparation globale avant la chirurgie. Après l'intervention, l'agitation avec vomissements et let signes d'amnésie rétrograde ont été plus fréquents avec le lorazepam.

EINE VERGLEICHSTUDIE VON LORMETAZEPAM UND TRIMEPRAZIN ALS ORALE PRÄMEDIKATION IN DER PÄDIATRISCHEN ANASTHESIE

ZUSAMMENFASSUNG

Hundert neun und neunzig Kindern erhielten entweder Lormetazepam 0,05 mg kg^{-1} oder Trimeprazin 3 mg kg^{-1} als orale Prämedikation in einer Doppelblindstudie. Lorazepam war angenehmer einzunehmen und führte eine bessere Stimmung hierbei, besass aber keine signifikanten Vorteile in der präoperativen Gesamtbeurteilung. Nach der Operation traten bei Lorazepam häufiger Unruhe mit Erbrechen und retrograde Amnesie auf.

ESTUDIO COMPARATIVO DEL LORAZEPAM Y DE LA TRIMEPRAZINA PARA FINES DE PREMEDICACION ORAL EN LA ANESTESIA PEDRIATICA

SUMARIO

Se administraron, 0,05 mg kg^{-1} de lorazepam o 3 mg kg^{-1} de trimeprazina a ciento noventa y nueva niños, cual premedicación oral de doble anonimato. El lorazepam demostró ser más agradable al paladar y produjo una alegre aceptación, pero no mostró ventaja significativa alguna en lo tocante a la avaluación global anterior a la intervención. A raiz de la operación el lorazepam produjo más vómitos y evidencia de amnesia retrógrada.

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RECOVERY FROM DAY-CASE ANAESTHESIA: COMPARISON OF A FURTHER FOUR TECHNIQUES INCLUDING USE OF THE NEW INDUCTION AGENT DIPRIVAN

D. F. JONES

SUMMARY

Eighty unpremedicated patients received thiopentone and halothane, propanidid and fentanyl, diprivan (ICI 35 868) alone, or diprivan and fentanyl, each supplementing 66% nitrous oxide in oxygen. Diprivan alone, or in combination with fentanyl, resulted in a more rapid awakening than thiopentone and halothane, and significantly shorter recovery times than both thiopentone and halothane and propranidid and fentanyl. Administration of fentanyl with diprivan significantly reduced the total dose of the latter and all indices of recovery. Propanidid and fentanyl did not produce shorter overall recovery times than thiopentone and halothane but nausea and vomiting after operation were significantly increased when compared with the other techniques.

Diprivan (2,6 di-isopropyl phenol) is a new i.v. anaesthetic agent which has been shown to be effective and safe for induction of anaesthesia in animals (Glen, 1980) and man (Rogers et al., 1980). It compares favourably with methohexitone when used in incremental doses for short gynaecological procedures (Rutter et al., 1980). The drug is virtually insoluble in water at room temperature and is presented in a concentration of 10 mg ml^{-1} in 16% Cremophor EL. Propanidid is a eugenol derivative (Dundee and Clarke, 1964) which is metabolized by pseudocholinesterase. It is insoluble in water and is also formulated in Cremophor EL. The major advantage of propanidid has been held to be the rapid and complete recovery following its use (Conway and Ellis, 1970), which has led to favourable comparisons with other agents when used intermittently for short gynaecological procedures (Dundee and Clarke, 1964; Lind and Roland, 1969). Thiopentone and halothane with 66% nitrous oxide in oxygen is a widely used anaesthetic technique.

The method of Craig, Cooper and Sear (1982) was specifically designed to enable further studies to be precisely comparable to theirs, thus allowing new drugs or drug combinations to be directly compared with their results. The present studies were designed to allow direct comparison of the effects of di-isopropyl phenol and propanidid with those of Althesin, methohexitone and etomidate, with or without previous injection of fentanyl. The combined results of the two studies demonstrate the influence of an analgesic such as fentanyl on recovery from anaesthesia induced and maintained with a variety of induction agents.

PATIENTS AND METHODS

Eighty women aged between 16 and 50 yr (ASA Grades I or II) who were fit apart from their gynaecological complaints were studied. All gave informed consent to take part in the studies. The patients were visited before operation when the control, pre-anaesthetic values of the recovery tests were obtained. The tests used to assess recovery were identical with those described by Craig, Cooper and Sear (1982). The first, similar to the peg-board described by Vickers (1965), involved the use of a Kiddicraft postbox toy. The second test was the deletion of "p" described by Dixon and Thornton (1973). Assessment of recovery was performed by an independent assessor in a fashion identical to that described by Craig, Cooper and Sear (1982). No premedication was given. All patients underwent a short procedure involving dilatation of the cervix, which acted as a standard surgical stimulus. None of the patients underwent termination of pregnancy.

Patients were randomly allocated to four groups:

Group 1 received thiopentone 4 mg kg^{-1}; anaesthesia was then maintained with 1.5% halothane and 66% nitrous oxide in oxygen.

Group 2 received fentanyl 100 µg followed by propanidid 7 mg kg^{-1} and increments of 50 mg to supplement 66% nitrous oxide in oxygen.

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Group 3 received diprivan 1.5 mg kg^{-1} and increments of 10 mg to supplement 66% nitrous oxide in oxygen.

Group 4 received fentanyl 100 µg followed by diprivan 1.5 mg kg^{-1} and increments of 10 mg to supplement 66% nitrous oxide in oxygen.

Propanidid alone with nitrous oxide was abandoned as a pilot study of five patients yielded unsatisfactory surgical conditions, mainly caused by hypertonus.

The use of diprivan had been approved by the Committee for Safety of Medicine and the relevant Hospital Ethics Committee before starting the trial. Patients who had a history of atopy or who had previously been anaesthetized with an agent formulated in Cremophor were excluded from the trial.

Patients were induced with the i.v. hypnotic agent administered over 30 s. Where the patient had been randomly allocated to receive fentanyl 100 µg, this was given just before the induction agent. Anaesthesia was maintained by 66% nitrous oxide in oxygen given by face-mask and Bain circuit. This was supplemented in group 1 by 1.5% halothane and in the other groups by increments of the hypnotic agent given when indicated clinically. At the end of the surgery, nitrous oxide was discontinued and the time noted.

RESULTS

The 20 patients in each group were comparable for age, weight and height. Duration of anaesthesia was approximately 8 min (table I).

The distribution of recovery times was skewed and statistical analyses were therefore performed on logarithmically transformed data. Table II shows the three indices of recovery with 95% confidence limits indicating the nature and direction of the skew. One patient in group 2 (propanidid/fentanyl) developed hypertonus which required a change of anaesthetic technique. The recovery results in this group were therefore derived from 19 patients instead of the 20 patients in groups 1, 3 and 4.

Patients in group 1 (thiopentone/halothane) took significantly longer to open their eyes and give the correct date of birth than those in the other three groups. However, recovery times of patients in group 2 (propanidid/fentanyl) were not significantly different from those in group 1 when assessed by the "post box" method. Patients in groups 3 and 4 (diprivan alone or with fentanyl) recovered in a significantly shorter time than the other two groups when assessed by the "post box" method. Fentanyl administered before diprivan (group 4) reduced the incremental dose of the latter by 47% ($P < 0.01$) and significantly decreased recovery times at all stages. Group 4 also showed the least variability, with narrower 95% confidence limits for the post box test. There were no significant changes in the p test scores between groups immediately after completion of the post box test.

More complications were observed in patients who received propanidid (table III). Severe hypertonus in one patient led to the technique being abandoned. Apart from this, nausea and vomiting was the most important complication in this group (13 of 19 patients) together with a general feeling of malaise compared with patients in the other three groups. Metoclopramide 10 mg was administered when required to suppress nausea and vomiting.

Pain on injection was a feature of groups 3 and 4 (diprivan), injection being in all cases performed through a 21-gauge needle to a vein on the dorsum of the hand. This pain was judged severe by three patients. However, no damage to the peripheral veins could be detected after operation. No incidents clinically suggestive of hypersensitivity reactions occurred during the trial.

TABLE I. *Patient age, weight and height of the groups with the duration of anaesthesia and total dose of hypnotic agent given (mean ± SEM)*

	Group			
	1	2	3	4
Age (yr)	36.1 ± 2.4	36.1 ± 1.3	35.9 ± 1.4	35.6 ± 1.8
Weight (kg)	60.3 ± 1.3	57.7 ± 1.8	59.1 ± 2.2	61.5 ± 1.6
Height (cm)	161.7 ± 1.2	159.5 ± 1.1	159.4 ± 1.6	161.6 ± 1.0
Duration (min)	8.4 ± 0.5	8.3 ± 0.4	7.8 ± 0.4	8.2 ± 0.5
Total dose (mg)	244 ± 6	737 ± 34	207 ± 12	154 ± 6

TABLE II. *The mean values of the three indices of recovery in minutes ± 95% confidence limits.* * P < *0.02;* ** P < *0.01;* *** P < *0.001; n.s. = not significant*

	Group 1	Group 2	Group 3	Group 4
				**
Time to opening eyes (min)	7.2 (2.5–21.1)	2.0 (0.5–7.7)	4.8 (1.9–10.4)	2.8 (0.8–9.4)
		***	**	***
				*
Time to giving correct date of birth (min)	9.1 (4.5–18.5)	3.1 (0.7–14.0)	5.8 (2.6–12.8)	3.6 (0.9–15.0)
		***	***	***
				**
Time to completing post box test (min)	35.3 (16.6–75.0)	37.2 (14.9–92.9)	23.0 (10.1–52.3)	15.4 (7.0–33.9)
		n.s.	**	***

No significant correlation was found in any of the groups between the times of recovery and the age or weight of the patient, the duration of the procedure, or the total dose of the hypnotic agent.

DISCUSSION

The objectives of outpatient anaesthesia are: a safe technique, adequate analgesia and amnesia throughout, few anaesthetic side-effects and rapid arousal (Urbach and Edelist, 1977).

The method of assessing recovery has been fully discussed by Craig, Cooper and Sear (1982). Comparison at the post box recovery stage shows no significant difference between their best two groups (methohexitone alone and Althesin alone) and group 1 (thiopentone/halothane). The latter technique is safe in the healthy patient and the contraindications are well defined, notably porphyria, recent exposure to halothane and procedures requiring maintenance of uterine muscle tone. The known tendency of patients to fall asleep again following initial recovery (Carson, 1975) and the "hang-over" effect resulting from the slow rate of metabolism of thiopentone must be taken into account. Methohexitone is more rapidly metabolized and might be expected to pro-

TABLE III. *Complications in the four groups of patients.* n = *20 patients.* †*Technique abandoned;* **of 19 patients*

	Group 1	Group 2	Group 3	Group 4
Pain on injection (no. patients)	0	0	9	5
Hypertonus	0	1†	0	0
Vomiting	1	8*	0	0
Nausea alone	0	5*	1	0
Headache	3	7*	0	0
Total of all complications	4	21	10	5

duce less long-term sedation, but is contraindicated in patients with seizure disorders.

Propanidid, Althesin and diprivan are all formulated in Cremophor EL and all have been implicated in hypersensitivity reactions. These agents are probably best avoided in patients who have previously received anaesthetic drugs formulated in Cremophor EL or any unknown anaesthetic within a short period of time, or who are likely to receive multiple anaesthetic administrations in the near future. They should also be used with caution in patients with a known history of allergic reactions to other drugs. The increased risk associated with any drug formulated in Cremophor EL must be justified by significant advantages.

Diprivan, especially when used with fentanyl, allowed significantly quicker recovery than any of the other groups tested, with minimal side-effects. Most patients given this agent remarked upon their clear-headedness and feeling of well-being after operation and considered the pain on injection to have been only a minor inconvenience. No patients given diprivan vomited after operation and only one was nauseated. Propanidid, despite its rapid metabolism, had no advantage over thiopentone and showed a significant frequency of side-effects, with eight of 19 patients vomiting and a further five feeling nauseated (combined total of 68.4%). Propanidid has also been shown to exert a considerable hypotensive effect in hypertensive patients (Prys-Roberts et al., 1971).

In conclusion, diprivan allows more rapid and complete recovery with fewer side-effects following day case anaesthesia when assessed by these methods. Other techniques tested appear to have little advantage over thiopentone and halothane except in circumstances where the latter is contraindicated. It is debatable whether the continued use of propanidid is justified.

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REVEIL D'UNE ANESTHESIE AMBULATOIRE: COMPARAISON DE QUATRE AUTRES TECHNIQUES DONT L'UTILISATION DU NOUVEL AGENT D'INDUCTION, LE DIPRIVAN

RESUME

Quatre-vingt patients non prémédiqués ont reçu du pentothal et de l'halothane, du propanidide et du fentanyl, du diprivan (ICI 35 868) seul ou du diprivan avec du fentanyl, chacun associé à 66% de protoxyde d'azote dans l'oxygène. Le diprivan seul ou associé au fentanyl, s'accompagne d'un réveil plus rapide que le pentothal et l'halothane, et de temps de récupération significativement plus brefs que le pentothal et l'halothane mais aussi que le propanidid et le fentanyl. L'administration de fentanyl associé au diprivan diminue significativement la dose totale de ce dernier et tous les indices de récupération. Le propanidide et le fentanyl ne s'accompagnent pas de temps de récupération globalement plus brefs que le pentothal et l'halothane, mais les nausées et les vomissements postopératoires sont significativement plus nombreux qu'avec les autres techniques.

AUFWACHPHASE BEI AMBULANZ-ANASTHESIE: VERGLEICH VON VIER WEITEREN TECHNIKEN EINSCHLIESSLICH DES NEUEN EINLEITUNGSMITTELS DIPRIVAN

ZUSAMMENFASSUNG

Achtzig unprämedizierte Patienten erhielten Thiopental und Halothan, Propanidid und Fentanyl, Diprivan alleine oder Diprivan mit Fentanyl, und in allen Fällen 66% Lachgas in Sauerstoff. Diprivan alleine oder in Kombination mit Fentanyl führte zu einem schnelleren Erwachen als Thiopental und Halothan und zu signifikant kürzeren Aufwachzeiten sowohl nach Thiopental–Halothan als auch nach Propanidid–Fentanyl. Die Verwendung von Fentanyl mit Diprivan setzte signifikant die

Gesamtdosis des letzteren herab und verkürzte alle Anzeichen der Aufwachphase. Propanidid und Fentanyl führten insgesamt nicht zu kürzeren Aufwachzeiten als Thiopental und Halothan; aber Übelkeit und Erbrechen nach der Operation nahmen in Vergleich zu anderen Techniken signifikant zu.

RECUPERACION DE ANESTESIA EN CASOS DE UN DIA: COMPARACION DE CUATRO TECNICAS ADICIONALES, INCLUSIVE EL USO DEL NUEVO AGENTE DE INDUCCION DIPRIVAN

SUMARIO

Se administró a ochenta pacientes sin premedicación tiopentona y halotano, propanidido y fentanilo, dipriván (ICI 35 868) solo, o dipriván y fentanilo, cada uno como suplemento de un 66% de óxido nitroso en oxígeno. El dipriván solo o en combinación con el fentanilo, resultó en un despertar más rápido que con la tiopentona y halotano, y con tiempos de recuperación significativamente más cortos que ambas combinaciones, tiopentona y halotano o propanidido y fentanilo. La administración de fentanilo con dipriván redujo de manera significante la dosis total de este último y todos los índices de recuperación. El propanidido y fentanilo no produjeron tiempos de recuperación globales más cortos que los de la tiopentona y halotano, pero aumentaron de manera marcada las nauseas y los vómitos después de la operación, si se comparan con las demás técnicas.

Br. J. Anaesth. (1982), 54, 635

CHANGES IN FETAL TCPO$_2$ VALUES OCCURRING DURING LABOUR IN ASSOCIATION WITH LUMBAR EXTRADURAL ANALGESIA

R. J. WILLCOURT, J. C. PAUST AND J. T. QUEENAN

SUMMARY

Forty-six of 64 high risk labours were managed with continuous lumbar extradural analgesia. Fetal heart rate (FHR) and continuous transcutaneous $P\text{O}_2$ (tc$P\text{O}_2$) measurements were made in the 64 patients. Abnormal fetal heart rate patterns and low tc$P\text{O}_2$ values associated with the onset of the extradural block were noted in 9% of these cases. A decrease in maternal arterial pressure and uterine hypertonus appeared to be responsible, singly or in combination, for the changes. These effects and the changes in FHR were not seen in the 18 mothers not receiving extradural analgesia. The supine position was associated with slightly smaller fetal tc$P\text{O}_2$ values than the preferred lateral positions, with a significant worsening of the fetal tc$P\text{O}_2$ values after induction of the extradural block although, overall, extradural analgesia neither improved nor impaired the fetal tc$P\text{O}_2$.

Continuous lumbar extradural analgesia has been reported to improve (Pearson and Davies, 1974) and to impair (Schifrin, 1972) fetal acid–base status in the first stage of labour when compared with infants of mothers not receiving extradural blockade. The circumstances which influence the fetus are changes in uteroplacental perfusion (Schifrin, 1972; McDonald, Bjorkman and Reed, 1974; Pearson and Davies, 1974; Jouppila et al., 1977) and the degree to which the acid–base state of the mother is altered. Changes in fetal heart rate (FHR) have occurred with the use of local analgesic agents and it was our intention to determine whether these changes were associated with alterations in the degree of fetal oxygenation.

PATIENTS AND METHODS

Sixty-four patients in spontaneous labour were studied, 46 of whom received continuous lumbar extradural analgesia. All mothers and their fetuses were monitored using the transcutaneous $P\text{O}_2$ technique. Twelve patients did not receive extradural analgesia because they were assessed initially as having FHR patterns suggestive of moderate fetal hypoxaemia. These patients were observed carefully and were found, on subsequent reassessment, to be comparable to the group initially selected for extradural analgesia. These patients were used as controls in addition to a further six patients randomly allocated to the non-extradural group since their initial assessment did not contraindicate the use of this form of analgesia. Thus 18 patients, comparable clinically to the 46 treated patients, were used for comparison. In addition, comparisons were made within the extradural group, before and after the administration of the analgesic agent.

The mothers had been classified as "high-risk" because of evidence of pre-eclampia, hypertension or diabetes, with some fetuses having substantial intrauterine growth retardation, abnormal antepartum fetal heart rate (FHR) tests, or being pre- or post-term. Twenty-eight fetuses of the 46 mothers selected for extradural analgesia had FHR abnormalities. Eighteen fetuses had mild to moderate variable decelerations, 10 had loss of beat-to-beat variability alone or in combination with occasional decelerations. All fetuses were in the cephalic presentation. The gestational ages as derived from the last menstrual period or by serial measurements of biparietal diameter were 36–42 weeks. Continuous lumbar extradural analgesia was commenced in the active phase of labour, with cervical dilatation of between 4 and 8 cm. Maternal arterial pressure (AP), intrauterine pressure (IUP), FHR and maternal and fetal tc$P\text{O}_2$ were measured.

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The patients were preloaded with lactated Ringer's solution 500–1000 ml and placed in the left lateral position. Using a mid-line approach and loss of resistance with a 10-ml syringe containing air to identify the extradural space, a test dose of 1.5% lignocaine 1–2 ml was given. Bupivacaine 0.5% without adrenaline was then injected to the extradural space, the definitive dose depending on the weight, height and age of the patient, satisfactory pain relief being the end-point. The patients were then placed supine for 8–10 min, after which they were transferred to the left lateral position.

After injection of the analgesic agent, measurements of systolic and diastolic arterial pressures were obtained using a mercury sphygmomanometer every 2 min for 20 min and then every 5 min for 10 min. The sensory level affected by the extradural block was noted.

The transcutaneous $P\mathrm{O}_2$ (tc$P\mathrm{O}_2$) electrode was applied to the fetal head as described by Huch and colleagues (1977). The tc$P\mathrm{O}_2$ of the mother and fetus were recorded on a Litton Oxymonitor (Litton Medical Electronics, Elk Grove, Illinois). The FHR and uterine contractions (UC) were recorded on either a Corometrics 101B (Corometrics, Wallingford, Connecticut) or a Sonicaid FM3R (Sonicaid, Fredericksburg, Virginia) fetal monitor. All data were transferred to a Hewlett–Packard multichannel recorder HP7758A (Hewlett–Packard, Waltham, Massachusetts). Blood-gas tensions from umbilical cord blood were measured on a Corning 165 analyser (Corning, Medfield, Massachusetts).

The definitions of the FHR patterns follow the criteria of Hon and Quilligan (1967). The normal range for the fetal tc$P\mathrm{O}_2$ is yet to be established, but published data (Huch et al., 1977; Willcourt et al., 1981) indicate that a range of 2–3.3 kPa is associated with fetal well being.

RESULTS

One hundred and sixty-six hours of fetal tc$P\mathrm{O}_2$ measurements were obtained from the 64 labours; 53 of these from labours in which extradural analgesia was not used. Non-recurring late decelerations with exaggerated FHR variability occurred five times in four fetuses during the 113 h of extradural analgesia, but were not seen in the 53 h without the extradural blockade. Two of the four fetuses were in the group that did not demonstrate any FHR abnormalities before blockade, one fetus had diminished FHR variability and the fourth fetus had demonstrated occasional mild variable decelerations before induction of the extradural block. Following the sudden severe decelerations that were temporally related to the onset of the extradural block, each fetus demonstrated a return to the previous FHR pattern.

Although the supine position generally decreased fetal tc$P\mathrm{O}_2$ by 0.27 kPa, the decrease was as great as 0.8 kPa in three fetuses, but excluding the four instances reported above, these changes were not associated with fetal distress. All other fetal tc$P\mathrm{O}_2$ values were essentially unaltered by extradural analgesia. The two lateral positions were compared before and after the onset of the block and were found to give comparable fetal tc$P\mathrm{O}_2$ values. In 18 of the 46 mothers, the right lateral position gave greater tc$P\mathrm{O}_2$ values than the left before the block, with changes of 0.27–0.4 kPa after blockade. The left lateral position was associated with greater fetal tc$P\mathrm{O}_2$ values than the right in 28 patients before and after the extradural block (table I). The better of two lateral positions is referred to as the "preferred" lateral position.

In the first patient with abnormal changes, a decrease in the fetal tc$P\mathrm{O}_2$ from 2.13 to 1.46 kPa occurred after the mother had been placed in the supine position (fig. 1). A further decrease occurred 8 min after the administration of the extradural analgesic. The uterine contractions as measured by an internal pressure catheter became more frequent and, although less intense than before the blockade, caused the uterine pressure to remain between 2.7 and 4 kPa for 5 min (normal 0.67–2.7 kPa). The FHR deceleration was accompanied by a decrease in tc$P\mathrm{O}_2$ which began to recover after the uterine contractions had ceased. However, a sustained pattern of contraction recurred, and decreases in FHR and tc$P\mathrm{O}_2$ were noted. The maternal arterial pressure (AP) decreased from 122/80 mm Hg to

TABLE I. *Effects of position and continuous lumbar extradural analgesia on fetal* tc$P\mathrm{O}_2$ *(kPa). The lateral position in this table refers to that side which gave the greater fetal* tc$P\mathrm{O}_2$ *values.* n = *number of observations made in each position after allowing 10 min for stabilization. Statistical analysis was performed using a two-tailed* t *test: Supine* v. *lateral* = $P < 0.1$ *(n.s.); lateral* v. *lateral extradural* = $P < 0.1$ *(n.s.); supine extradural* v. *lateral extradural* = $P < 0.001$

	Supine	Lateral	Supine extradural	Lateral extradural
Range	1.87–2.8 (n = 19)	1.87–3.73 (n = 19)	1.06–2.4 (n = 20)	2.0–4.0 (n = 20)
Mean ± SD	2.4 ± 0.2	2.5 ± 0.4	1.6 ± 0.28	2.67 ± 0.45

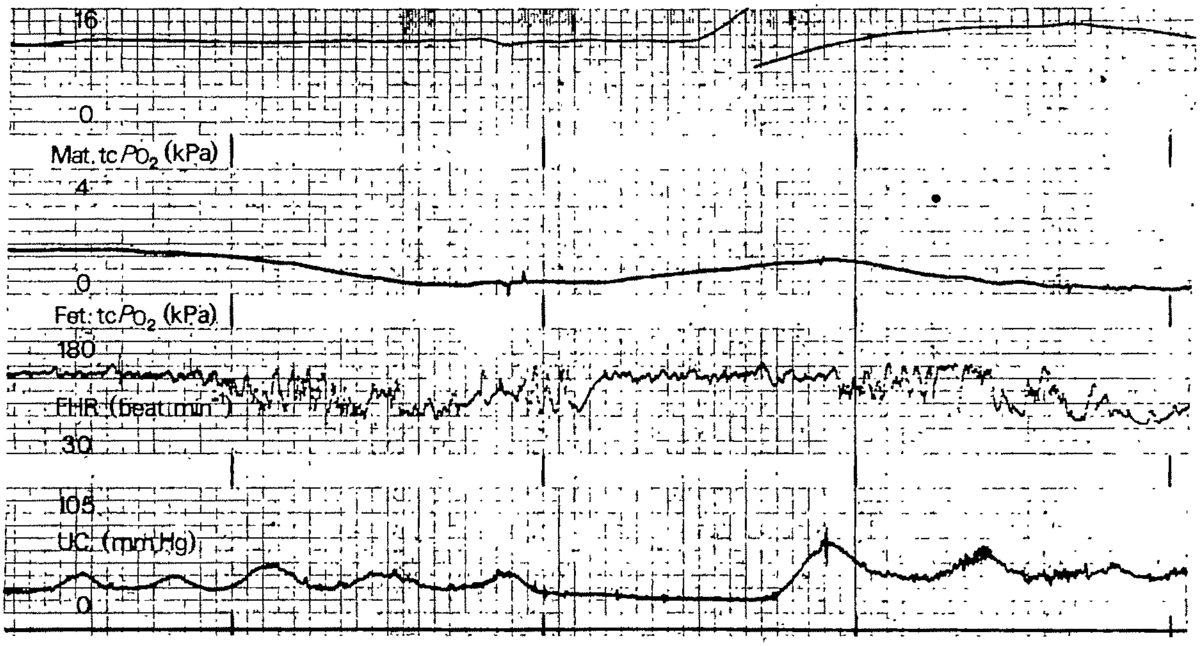

FIG. 1. First patient: Records of maternal transcutaneous PO$_2$ (Mat. tc$P$O$_2$), fetal transcutaneous PO$_2$ (Fet. tc$P$O$_2$), fetal heart rate (FHR) and uterine contractions (UC). Injection of analgesic 8 min before onset of fetal bradycardia.

90/55 mm Hg during the first deceleration. Oxygen was administered to the mother, she was placed in the right lateral position and the rate of fluid infusion increased, whereupon improvement was seen in FHR and tc$P$O$_2$. The fetus was delivered 1 h later with an umbilical artery (UA) pH of 7.24 unit and Apgar scores of 8 at 1 min and 9 at 5 min. Gestational age was assessed as being 39 weeks.

In the second patient (fig. 2), following administration of the definitive dose of analgesic, exaggerated FHR variability was observed and was followed by a late deceleration occurring in association with a decrease in fetal tc$P$O$_2$. The intrauterine pressure tracing showed a "coupling" pattern with a low resting pressure. Oxygen was administered to the mother before the deceleration in fetal heart rate. There was no significant change in the maternal arterial pressure at any time during the FHR deceleration (AP 110/76–115/75 mm Hg). Umbilical artery pH was 7.26 unit and Apgar scores were 7 at 1 min and 9 at 5 min. The fetus was assessed as being 41 weeks.

In the example shown in figure 3, exaggerated FHR variability occurred with a decrease in the fetal tc$P$O$_2$ 13 min after the regional block. The intrauterine pressure increased and remained increased for 8 min during which further changes in FHR and fetal tc$P$O$_2$ were seen. The maternal AP changed slightly from 130/84 to 120/78 mm Hg.

The position of the mother was changed from the right to the left lateral position and the rate of infusion increased. This mother was already breathing oxygen, but because of the poor application of the mask the maternal tc$P$O$_2$ values were not as high as expected. Following a further injection of 0.5% bupivacaine into the extradural space, the same sequence of events occurred. Thirty minutes later the baby was delivered. The UA pH was 7.16 unit and the Apgar scores were 6 at 1 min and 8 at 5 min. Compression of the fetal tc$P$O$_2$ electrode resulted in erroneously low tc$P$O$_2$ values at delivery. Gestational age was 41 weeks by dates.

The changes seen in the fourth patient (fig. 4) are similar to those already described, but the fetal tc$P$O$_2$ changes were not as marked. The uterine contractions were, however, recorded by an external tocodynamometer so that changes in intrauterine pressure could not be appreciated or quantitated.

Exaggerated FHR variability was seen with a decrease in fetal tc$P$O$_2$. The maternal arterial pressure decreased from 114/72 to 98/58 mm Hg during the period of abnormal fetal recording. This 39-

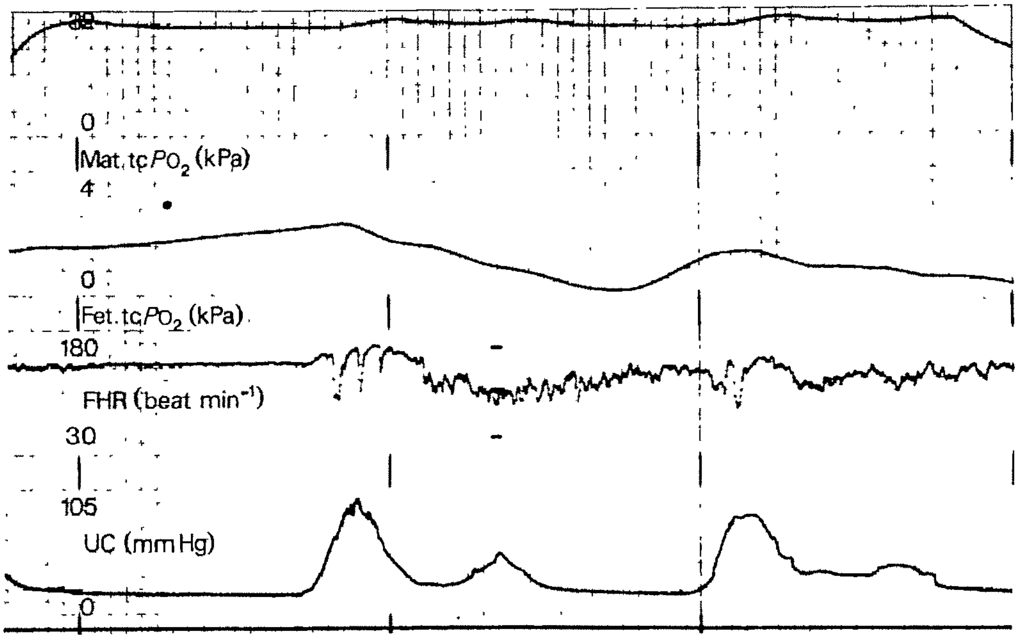

FIG. 2. Second patient: Legends as in figure 1. Analgesic administered 10 min before changes in fetal heart rate.

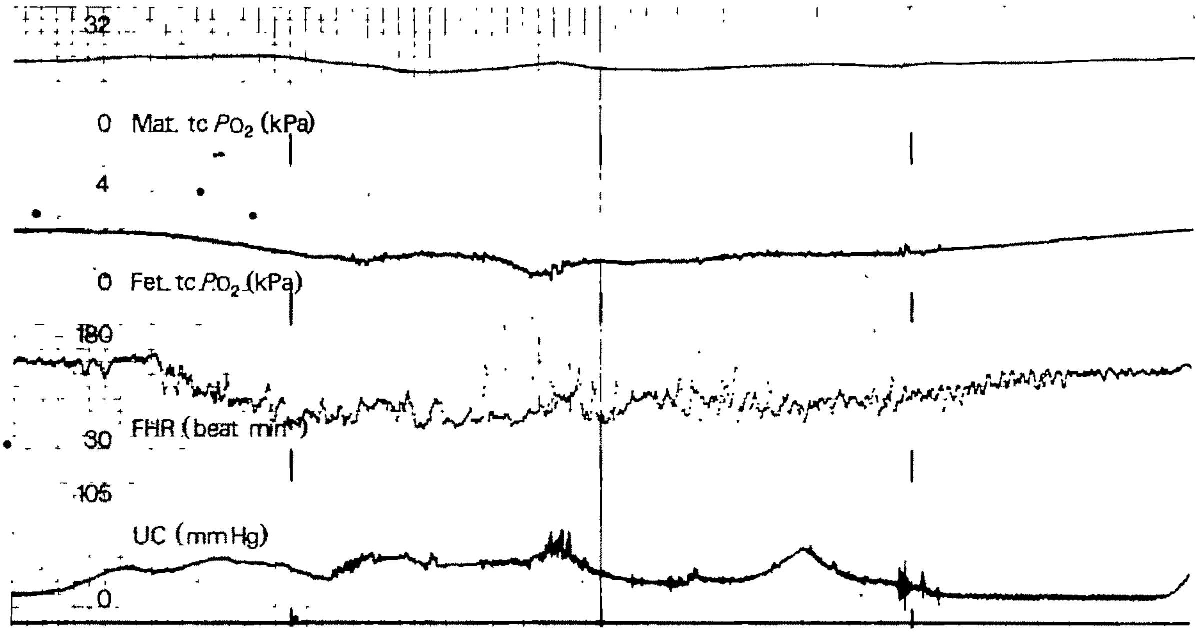

FIG. 3. Third patient: Legends as in figure 1.

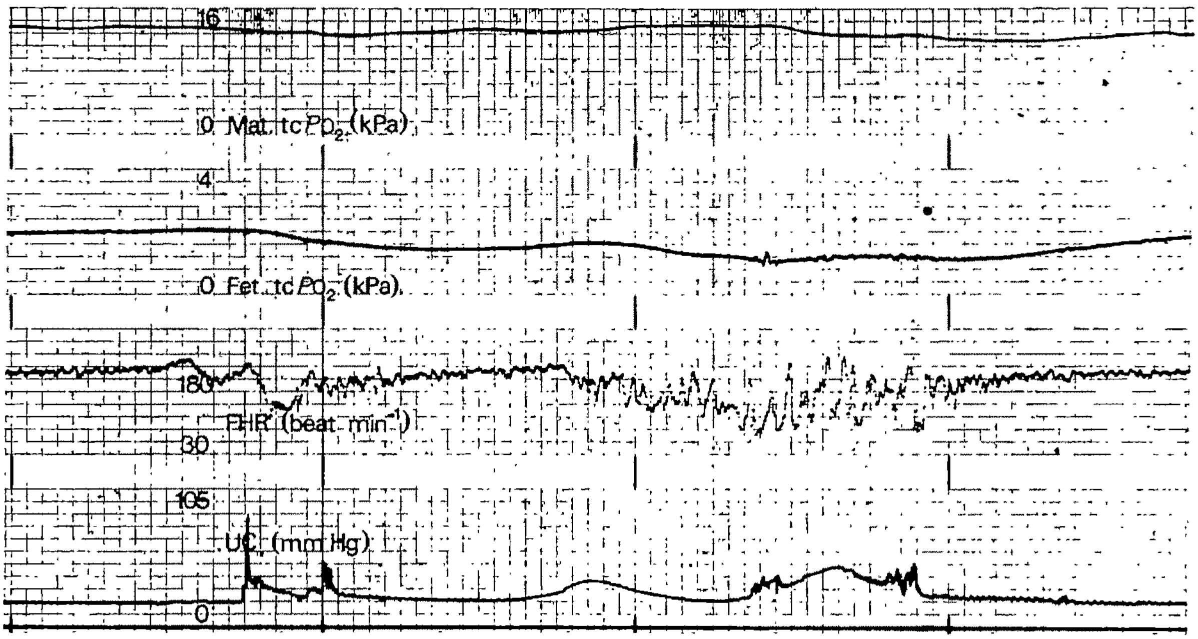

FIG. 4. Fourth patient: Legends as in figure 1.

week fetus had a UA pH of 7.21 unit and the Apgar scores were 8 at 1 min and 8 at 5 min.

In all instances the mothers were in the supine position when the FHR abnormalities occurred.

DISCUSSION

Continuous lumbar extradural analgesia is a preferred method of pain relief in many obstetric centres. The hazards of the technique for the fetus are well recognized and relate primarily to changes in the utero-placental circulation, to toxic effects of the drugs on the fetus (Schifrin, 1972; Pearson and Davies, 1974; McDonald, Bjorkman and Reed, 1974) and, secondarily, to malpresentations of the fetus (Hoult, MacLennan and Carrie, 1977).

A decrease in blood flow in the utero-placental circulation occurs by redistribution of the maternal intravascular compartment with decreases in venous return and vasoconstriction above the block, or by an increase in intrauterine tone, or both (McDonald, Bjorkman and Reed, 1974; Malthau, 1975). It has been postulated that when the block is below T10, this effect is decreased (Abouleish, 1976). Maintenance of a supine position further aggravates the already compromised uteroplacental circulation, increasing the chances of fetal distress.

These observations of 46 labours managed under extradural blockade show five instances in four fetuses of fetal bradycardia with changes in fetal tcPo_2 and in the pattern of uterine contraction, temporally related to the administration of extradural analgesia. While 28 of the 46 patients who received extradural analgesia had fetuses with abnormal FHR patterns before blockade, this particular type of deceleration was seen only in close relationship to the administration of the extradural analgesic. A decrease in the fetal tcPo_2 accompanied the changes in FHR with a return to the previous tcPo_2 values once the episode had passed. Clearly, avoidance of the supine position is essential if the frequency of fetal hypoxaemia is to be decreased. Alternately placing the mother in the right or left lateral position while waiting for the block to become established would seem preferable to keeping the mother supine. Otherwise, the effects of the extradural analgesia were neither to improve nor impair the fetal tcPo_2 values provided the mothers were in the preferred lateral position. The supine position was always associated with a lower value than the lateral positions with the effect more pronounced after institution of the block.

The frequency of fetal bradycardia and lower fetal tcPo_2 values in our study was 9% (four out of 46). Maltau (1975) in reviewing other studies cited a frequency of fetal distress of between 10 and 77%, while he had a 6% frequency in his own study.

Despite being placed in the supine position those patients in the non-treated group did not exhibit the type of FHR deceleration observed in our study.

Two of the four mothers did not show a hypotensive episode in association with the changes in FHR and fetal tcP_{O_2}. Pooling of blood in the lower extremities with aorto–caval compression may not always result in changes in arterial pressure in the upper extremities, even though utero–placental blood flow is impaired. Uterine hyperactivity was evident in one of these patients and was seen during a hypotensive episode in another. Therefore, alone or in combination, maternal hypotension and uterine hypertonicity seemed to be responsible for the FHR and fetal tcP_{O_2} changes recorded.

In patient three, low values of fetal tcP_{O_2} were recorded for 1.5 h despite a return to a normal FHR pattern and in the absence of overt maternal hypotension. Spuriously low tcP_{O_2} values may be seen if the electrode is compressed against the pelvic tissues. A vaginal examination showed that this was not the case. Further, there was no clinical evidence for direct intravascular injection of the local analgesic. Because this was an investigative study and the FHR was used as the guide to management rather than the fetal tcP_{O_2}, labour was permitted to progress. However, the two episodes of profound hypoxaemia and the subsequent lowering of the overall fetal tcP_{O_2} values were probably not spurious results, as indicated by the fetal acidosis noted at delivery. This also suggests that continued fetal hypoxaemia may not be reflected in the FHR pattern in all instances. In repeated episodes of severe bradycardia associated with extradural analgesia fetal scalp blood sampling may be helpful.

Because of the potential for causing impaired utero–placental perfusion, it would seem prudent to discontinue an oxytocic infusion before establishing extradural analgesia. The decreasing of uterine activity at the time of onset of the block may avoid some instances of fetal distress. The oxytocic infusion could be restarted once the mother and fetus are stable. The appearance of severe fetal bradycardia within a short time of the induction of extradural analgesia should suggest impairment of the utero–placental circulation. Corrective measures include lateral positioning of the mother, an increase in the rate of infusion of the i.v. fluids and oxygen by face-mask. The fetal distress will resolve with restoration of the utero–placental circulation.

Our low rate of fetal hypoxaemia following extradural analgesia in a group of "high-risk" patients suggests that measures to avoid fetal circulatory impairment are generally successful. Fetal hypoxaemia was always associated with a deceleration of the FHR, although persistent low tcP_{O_2} values were not always reflected in the FHR pattern. Therefore, FHR monitoring should be used before initiating the extradural blockade so that hypoxaemia may be recognized.

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MODIFICATIONS DE LA P_{O_2} TRANSCUTANEE FOETALE AU COURS DU TRAVAIL ASSOCIE A UNE ANALGESIE PERIDURALE LOMBAIRE

RESUME

Parmi 64 travaux de grossesses à haut risque, 46 ont été effectués sous analgésie péridurale lombaire continue. Des mesures en continu de la fréquence cardiaque (FCF) et de la P_{O_2} transcutanée (tcP_{O_2}) du foetus ont été faites chez les 64 patientes. Dans 9% de ces cas sont apparues des courbes anormales de fréquence cardiaque du foetus et une diminution de la tcP_{O_2} au moment de l'installation du bloc péridural. La diminution de la pression artérielle de la mère et l'hypertonie utérine ont été rendues responsables, isolées ou en association, de ces modifications. Ces effets et les changements de FCF, n'existaient pas chez les 18 mères qui n'avaient pas d'analgésie péridurale. Le décubitus dorsal entrainait des valeurs de tcP_{O_2} foetale légèrement inférieures aux décubitus latéraux préférentiels, avec une aggravation significative des valeurs de tcP_{O_2} foetale après l'induction du

bloc péridural. Cependant dans l'ensemble, l'analgésie péridurale n'a ni amélioré ni détérioré la tc$P\text{O}_2$ foetale.

VERÄNDERUNGEN DER FOETALEN TRANSKUTANEN $P\text{O}_2$ WERTE UNTER DER GEBURT IN VERBINDUNG MIT LUMBALER PERIDURALANÄSTHESIE

ZUSAMMENFASSUNG

Bei 46 von 64 Risikogeburten führten wir eine Dauer-Periduralanästhesie durch und zeichneten bei allen die kindliche Herzfrequenz (KHF) und die kontinuierlichen transkutane $P\text{O}_2$ Werte (tc$P\text{O}_2$) auf. Abnormale kindliche Herzfrequenz und niedrige transkutane $P\text{O}_2$ Werte die in Verbindung mit dem Einsetzen des Peridural-Block auftraten, wurden bei 9% den Fälle gemessen. Ein Abfall des arteriellen Druckes bei der Mutter und Hypertonus des Uterus schien alleine oder mitverantwortlich für die Veränderungen zu sein. Diese Auswirkungen und Veränderungen der KHF waren bei den 19 Patienten ohne Periduralе nicht zu beobachten. Die Rückenlagerung war mit geringniedrigeren foetalen tc$P\text{O}_2$-Werten verbunden als die vorzugsweise verwendete Seintenlagen mit einer signifikanten Verschlechterung der foetalen tc$P\text{O}_2$ Werten nach Einsetzen des Peridural-Blocks. Alles in allem wurde durch den Epidural-Anästhesie die foetalen tc$P\text{O}_2$ Werte weder verbessert noch verschlechtert.

CAMBIOS EN LOS VALORES DEL TC$P\text{O}_2$ FETAL OCURRIDOS DURANTE EL PARTO EN ASOCIATION CON LA ANALGESIA EXTRADURAL LUMBAR

SUMARIO

Se administraron cuarenta y seis partos con analgesia extradural lumbar continua entre 64 partos muy arriesgados. Se llevaron a cabo las mediciones del ritmo cárdiaco fetal (FHR) así como del $P\text{O}_2$ (tc$P\text{O}_2$) transcutáneo continuo en las 64 pacientes. Se observaron contornos anormales del ritmo cárdiaco fetal y bajos valores del tc$P\text{O}_2$ asociados con la aparición del bloqueo extradural en un 9% de los casos. Una disminución de la presión arterial materna y del hipertono uterino pareció ser la causa, separada o conjuntamente, de los cambios. Estos efectos y cambios del FHR no se manifestaron en las 18 madres que no recibieron la analgesia extradural. La postura en decúbito supino se halló asociada con valores del tc$P\text{O}_2$ fetal más bajos que los encontrados en las posturas laterales preferidas, con un empeoramiento significativo de los valores del tc$P\text{O}_2$ fetal después de la inducción del bloqueo extradural, aunque, en total, la analgesia extradural ni mejoró ni empeoró el tc$P\text{O}_2$ fetal.

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PLACENTAL TRANSFER OF ORG NC45 IN WOMEN UNDERGOING CAESAREAN SECTION

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SUMMARY

Org NC45 60–80 $\mu g\,kg^{-1}$ was administered to 20 pregnant women undergoing general anaesthesia for Caesarean section. Org NC45 plasma concentrations were measured fluorimetrically in samples of maternal, venous and arterial cord blood obtained at delivery. The venous cord to maternal concentration ratio averaged 11% and was not influenced by the interval between induction and delivery. The venous cord plasma concentration averaged 40 $ng\,ml^{-1}$. The arterial cord concentration was less than the venous cord concentration in every instance and was undetectable in four patients. It is concluded that Org NC45 crosses the human placental barrier to a very limited extent and that its use during anaesthesia for Caesarean section is safe for the newborn.

Neuromuscular blocking agents do not cross the placenta readily because they are relatively insoluble in lipids and are highly ionized in plasma. Savage, Sleigh and Carlyle (1980) predicted that, on account of its chemical structure, Org NC45 might be more lipophilic than either pancuronium or tubocurarine. However, this hypothetical lipid solubility is low compared with the high water solubility of the drug. In addition, like most quaternary ammonium compounds, Org NC45 is insoluble in diethyl ether (Savage, Sleigh and Carlyle, 1980). However, since the placental transfer of Org NC45 may be greater than that of other neuromuscular blocking drugs, the present study was undertaken in women undergoing Caesarean section.

PATIENTS AND METHODS

Twenty pregnant women undergoing elective Caesarean section were included in the study. Consent for the administration of Org NC45 and the sampling of maternal venous and umbilical cord blood was obtained from each patient after the risks of the investigation had been explained. Anaesthesia was induced with thiopentone 5 $mg\,kg^{-1}$ i.v. and the trachea intubated following the administration of suxamethonium 1 $mg\,kg^{-1}$. Org NC45 4–6 mg, was injected to maintain neuromuscular blockade and anaesthesia was maintained with 60% nitrous oxide in oxygen delivered by intermittent positive pressure ventilation (minute ventilation 100 $ml\,kg^{-1}$). In eight patients 0.5% halothane was administered intermittently. The management of the newborn included assessment and recording of the Apgar scores at 1 and 5 min and preparation for ventilation. Maternal and cord blood samples were obtained simultaneously at delivery. A 10–20 cm section of the cord was secured between two clamps and venous and arterial blood samples withdrawn. Blood was collected in heparinized tubes and was centrifuged within 5 min of its collection. One millilitre of plasma was mixed in a tube containing 150 µlitre of sodium dihydrogen phosphate (NaH_2PO_4) 1 mol $litre^{-1}$ to prevent the hydrolysis of Org NC45 (Paanakker and Van de Laar, 1980). The tubes were kept at −20 °C until analysis. Org NC45 was assayed according to a modification of the Rose Bengal fluorimetric method used for the determination of pancuronium (Kersten, Meijer and Agoston, 1973). The lowest concentration that could be reliably determined was 25 $ng\,ml^{-1}$.

RESULTS

Org NC45 was found in detectable amounts in all venous cord blood samples. The venous cord concentration averaged 40 $ng\,ml^{-1}$ and was much lower than the maternal concentration (390 $ng\,ml^{-1}$). Individual values are detailed in table I. The venous to maternal concentration ratio was 11% and was not influenced by the interval between injection of Org

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TABLE I. *Individual values of umbilical and maternal concentrations of Org NC 45, induction–delivery interval and Apgar scores at 1 min and 5 min. The Org NC 45 value of zero means that the concentration is lower than the level of detection of 25 ng ml^{-1} — = not determined. A–D = interval between Org NC 45 administration and delivery*

	Org NC 45 concn (ng ml^{-1})			Apgar score		
Patient no.	Umbilical vein	Umbilical artery	Mother	1 min	5 min	A–D (min)
1	30	—	240	9	10	8
2	40	30	245	8	10	13
3	30	—	230	7	10	5
4	55	50	200	9	10	14
5	55	50	245	10	10	12
6	40	30	300	7	10	9
7	25	25	360	10	10	10
8	40	—	485	10	10	6
9	45	25	365	10	10	9
10	55	25	625	7	9	8
11	35	30	405	10	10	9
12	60	0	700	10	10	13
13	25	0	325	10	10	5
14	40	30	445	8	10	21
15	40	30	480	10	10	7
16	40	—	435	10	10	9
17	35	0	300	10	10	10
18	30	—	465	10	10	5
19	25	0	400	10	10	6
20	65	—	560	10	10	8

NC 45 and delivery. The concentration of Org NC 45 in the cord artery was always lower than in the cord vein: in four samples out of the 14 examined, Org NC 45 was not detectable. Apgar scores at 1 and 5 min averaged 9.1 and 9.9.

DISCUSSION

This study demonstrates that Org NC 45 crosses the human placental barrier to a very limited extent. In comparison with pancuronium, which possesses approximately the same potency as Org NC 45 (Agoston et al., 1980), the placental transfer of Org NC 45 is at least half. The fetal concentration of pancuronium averaged 70 ng ml^{-1} after the administration of equipotent doses of pancuronium to women undergoing Caesarean section (Booth, Watson and McLeod, 1977; Duvaldestin et al., 1978). Several factors may influence the placental transfer of foreign compounds: molecular weight, lipid solubility, the concentration gradient across the placental membrane and the duration of feto–placental exchange. Org NC 45 is believed to be more lipophilic than pancuronium, the latter being also more lipophilic than tubocurarine (Savage, Sleigh and Carlyle, 1980). However, this lipophilic property is weak compared with the hydrophilic property of all neuromuscular blocking drugs. This may partly explain why Org NC 45 does not cross the placenta more rapidly than pancuronium. Another factor influencing the placental transfer is the rate at which the drug disappears from the maternal plasma. Org NC 45 is eliminated rapidly from the plasma (Van der Veen and Bencini, 1980), a property which tends to decrease the concentration gradient across the placental membrane. A feto–maternal concentration ratio of 11% was observed for Org NC 45 whereas this ratio was of 22% for pancuronium (Booth, Watson and McLeod, 1977; Duvaldestin et al., 1978). The feto–maternal ratio did not correlate with the interval between injection of Org NC 45 and delivery as has been shown for dimethyl tubocurarine (Kivalo and Saarikoski, 1976) and pancuronium (Duvaldestin et al., 1978). Deacetylation of Org NC 45 by placental enzymes remains a possible explanation for its low concentration in the newborn. The arteriovenous concentration difference in the cord vessels suggests an extensive uptake of Org NC 45 by the fetus. The hepatic uptake of Org NC 45 contributes normally to its rapid elimination from the plasma and may be more important in the fetal liver which receives 50% of the umbilical blood flow. Therefore, fetal hepatic uptake will decrease the effects of any placental transfer since the arterial cord blood concentration reflects more accurately the concentration delivered to the muscle end-plates. The highest arterial cord concentration of Org NC 45 was 50 ng ml^{-1} and is much smaller than the concentration of 140 ng ml^{-1} which corresponds to a 50% neuromuscular block in adults (Van der Veen and Bencini, 1980).

We can conclude from this study that the fetus receives an insignificant proportion of any clinical dose of Org NC 45 received by the mother and that its use during obstetric anaesthesia is safe for the newborn.

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TRANSFERT PLACENTAIRE DE L'ORG NC 45 CHEZ DES FEMMES SUBISSANT UNE CESARIENNE

RESUME

De l'Org NC 45 à la dose de 60–80 μg kg^{-1} a été administré à 20 femmes enceintes recevant une anesthésie générale pour Césarienne. Les concentrations plasmatiques de l'Org NC 45 ont été mesurées par fluorimétrie dans des échantillons de sang maternel et de sang artériel et veineux du cordon lors de l'extraction. Le rapport entre les concentrations maternelle et veineuse dans le cordon, avoisinaient 11% et n'étaient pas influencées par le délai entre l'induction et l'extraction. La concentration plasmatique du sang veineux dans le cordon avoisinait 40 ng ml^{-1}. La concentration dans le sang artériel du cordon était plus basse que dans le sang veineux dans chaque cas et était non-dosable chez quatre patientes. Nous en concluons que l'e Org NC 45 traverse la barrière placentaire chez l'homme de façon très limitée et que son utilisation au cours de l'anesthésie pour Césarienne est sans danger pour le nouveau-né.

DIE DURCHTRITT VON ORG NC 45 DURCH DIE PLAZENTA BEI FRAUEN WÄHREND DES KAISERSCHNITTES

ZUSAMMENFASSUNG

Org NC 45 60–80 μg kg^{-1} wurde 20 schwangeren Frauen verabreicht, die sich einer Allgemeinnarkose wegen eines Kaiserschnittes unterziehen mussten. Die Org NC 45-Konzentration wurde fluorimetrisch in Proben von mütterlichem venösen und arteriellem bei der Entbindung gewonnenem Nabelschnurblut gemessen. Das Konzentrationsverhältnis von venösem Nabelschnurblut zum mütterlichen betrug im Durchschnitt 11% und änderte sich nicht zwischen Narkoseeinleitung und Entbindung. Die Plasmakonzentration im venosen Nabelschnurblut betrug im Durchschnitt 40 ng ml^{-1}. Die Konzentration im arteriellen war bei jeder Messung kleiner als die im venösen Nabelschnurblut und war bei vier Patienten unmessbar. Daraus ist zu schliessen dass Org NC 45 die menschliche Planzentarschränke in einem sehr begrenzten Aussmass überschreitet und daβ eine Verwendung bei der Narkose für den Kaiserschnitt für das Neugeborense sicher ist.

PASO DE LA BARRERA DE LA PLACENTA POR PARTE DEL ORG NC 45 EN MUJERES SOMETIDAS A OPERACION DE CESAREA

SUMARIO

Se administró de 60 a 80 μg kg^{-1} de Org NC 45 a 20 mujeres preñadas sometidas a anestesia general para fines de operación de cesárea. Las concentraciones de Org NC 45 en el plasma se midieron fluorimétricamente en muestras de sangre del cordón arterial y venoso de la madre, que se obtuvieron en el parto. La razón entre la concentración del cordón venoso y la concentración materna fue del 11% y no vino influenciada por el lapsus entre la inducción y el parto. El promedio de la concentración del plasma del cordón venoso fue de 40 ng ml^{-1}. La concentración del cordón arterial fue inferior a la del cordón venoso en todo momento y no pudo detectarse en cuatro de las pacientes. La conclusión es que el Org NC 45 cruza la barrera de la placenta humana, en cantidades muy limitadas y que su uso durante la anestesia tendente a la operación de cesárea es seguro para el recién nacido.

Br. J. Anaesth. (1982), 54, 647

DOSE–RESPONSE RELATION FOR ATRACURIUM, ORG NC45 AND PANCURONIUM

L. GRAMSTAD AND P. LILLEAASEN

SUMMARY

The potencies of atracurium, Org NC45 and pancuronium were determined using cumulative dose–response curves. The effective doses producing 95% twitch depression were 279 $\mu g\,kg^{-1}$, 56 $\mu g\,kg^{-1}$ and 64 $\mu g\,kg^{-1}$ respectively, the relative potency being 1:5.0:4.3. The calculated log-probit dose–response curves showed the steepest slope for pancuronium, although the slopes did not deviate significantly from the parallel. The three drugs provided equal and generally good intubating conditions at approximately 95% twitch depression. Greater arterial pressure and heart rate were seen with pancuronium than with atracurium and Org NC45.

Atracurium and Org NC45 are newly developed non-depolarizing neuromuscular blocking drugs which are reported to have intermediate durations of action. Cumulative effects seem to be lacking, and cardiovascular effects are either minimal or absent (Agoston et al., 1980; Crul and Booij, 1980; Coker et al., 1981; Payne and Hughes, 1981). A comparative study on atracurium and Org NC45 has not been performed and an estimation of their relative potencies is indicated before proceeding with more detailed clinical investigations.

PATIENTS AND METHODS

Thirty female patients, ASA class I, about to undergo gynaecological operations for non-malignant conditions, gave informed consent to the study. Patients were excluded from the study if: pregnant or in the puerperium, receiving medication for infectious or other diseases, body weight deviated by more than 20% from normal (Natvig, 1956), younger than 20 or older than 50 yr of age.

The patients were premedicated 1 h before anaesthesia with pethidine 75 mg and atropine 0.6 mg i.m. Anaesthesia was induced with diazepam 10 mg, fentanyl 0.2 mg and thiopentone 100–500 mg i.v. till the eyelash reflex was abolished, and maintained subsequently during the recordings with 50% nitrous oxide in oxygen using intermittent positive pressure ventilation via a face mask. The patients were randomly allocated to three groups, which received one of the neuromuscular blocking agents: atracurium, Org NC45 or pancuronium. All measurements were made before the start of surgery.

The left ulnar nerve was stimulated electrically at the wrist via subcutaneous needle electrodes connected to a Myotest stimulator (Viby-Mogensen et al., 1980) delivering supramaximal impulses at 0.1 Hz. The force of the adduction of the thumb was measured by a Statham UC3 transducer connected to a Hewlett–Packard 7702B recorder equipped with 8805C amplifier. Resting thumb tension was adjusted to 280 g before the recordings started, and was reassessed after the study to ensure that preload had been maintained between 200 and 300 g.

When the evoked twitch response was stable, the neuromuscular blocking drug was administered in incremental doses to obtain an individual dose–response curve for each patient, using the principles described by Donlon, Ali and Savarese (1974). Each drug was given as five equal increments, the first two increments being injected in one dose to avoid zero-effect. The sizes of the increments were determined from a preceeding pilot study on 20 patients who fulfilled the criteria detailed above. The cumulative doses were estimated to give four defined points for each drug on a dose–response curve, the last injection producing about 95% depression of the twitch. The increments were: atracurium 55 $\mu g\,kg^{-1}$, Org NC45 12 $\mu g\,kg^{-1}$ and pancuronium 13 $\mu g\,kg^{-1}$. After the injection of each dose, the twitch response was observed until a maximum effect was obtained, as judged by three consecutive twitches of equal height, before the next incremental dose was given.

When the maximum effect had been achieved after the last incremental dose, the trachea was

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intubated. Conditions for intubation were classified according to Lund and Stovner (1970).

At each increment arterial pressure was measured indirectly with a sphygmomanometer and heart rate was registered on an e.c.g. monitor. Mean arterial pressure was assumed to be diastolic pressure plus one-third pulse pressure (Kelman, 1971).

Depression of twitch height was statistically treated in probit values (Finney, 1952), and the presented mean responses are transformed probit means. The composite dose–response curve for each drug was determined by log-probit transformation of the data and calculation by the method of least squares. Other statistical analyses were by Student's *t* test. Statistical differences were considered significant at $P<0.05$.

RESULTS

The three groups of patients were of similar age, weight and body surface area (table I).

Mean responses of the four doses of the three drugs are presented in figure 1. Log-probit regression lines are drawn to show the cumulative dose–response relation for each drug. Calculated dose–response values are presented in table II. For 95% blocking doses (ED_{95}) the relative potency for atracurium, Org NC45 and pancuronium was 1:5.0:4.3. The difference in potency between Org NC45 and pancuronium was not significant. The slopes of the regression lines were similar and did not deviate significantly from each other.

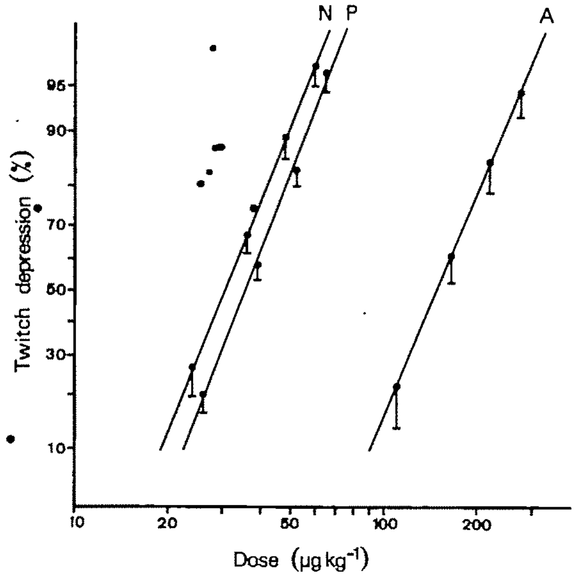

FIG. 1. Mean cumulative dose–response curves for Org NC45 (N), pancuronium (P) and atracurium (A). Mean twitch depression ± SEM after each incremental dose is indicated.

Conditions for intubation were similar with the three agents at maximum twitch depression (table III). Excellent intubating conditions were obtained when twitch depressions were most marked.

Average arterial pressure and heart rate were greater in the group receiving pancuronium than in the other two groups (fig. 2).

DISCUSSION

Since neuromuscular blockade has a quantal response to drug concentration the pharmacodynamics are suitably described by a log-probit dose–response relationship (Ginsburg, Kitz and Savarese, 1971). Construction of cumulative dose–response curves showed Org NC45 to be about 15% more potent than pancuronium and about five times more potent than atracurium for doses producing 95% depression of twitch response. The dose–response curves were parallel, making these relative potencies valid for other doses also.

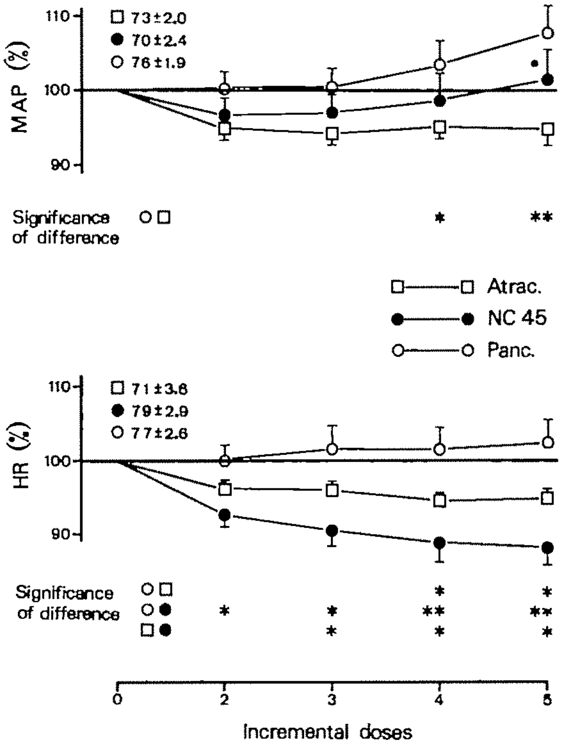

FIG. 2. Mean arterial pressure (MAP) and heart rate (HR) at the four dose–response levels. Mean results ± SEM are expressed as percentage of the control values. The absolute values of the latter are quoted on the figure at 0 dose as mean ± SEM. $^{*}P<0.05$; $^{**}P<0.01$.

TABLE I. *Characteristics of the patients*

Drug group	*n*	Mean age (yr ± SD)	Mean weight (kg ± SD)	Mean body surface (m^2 ± SD)
Atracurium	10	34.2 ± 4.0	58.9 ± 5.0	1.645 ± 0.083
Org NC45	10	34.6 ± 7.7	59.1 ± 5.1	1.665 ± 0.105
Pancuronium	10	32.5 ± 8.3	59.8 ± 4.6	1.653 ± 0.085

TABLE II. *Calculated mean dose–response values and their 95% confidence limits*

Drug	ED$_{50}$ ($\mu g\ kg^{-1}$)	ED$_{95}$ ($\mu g\ kg^{-1}$)	Curve slope (probit log^{-1})
Atracurium	147.7 (116.7–186.9)	279.3 (235.5–331.1)	5.95 (5.02–6.87)
Org NC45	30.3 (25.6–35.8)	56.2 (48.4–65.2)	6.12 (5.19–7.05)
Pancuronium	35.7 (31.9–39.8)	64.4 (57.7–71.8)	6.41 (5.78–7.05)

TABLE III. *Intubating conditions and the corresponding maximum twitch depressions (%). The latter are given as means and total range*

	Intubating conditions		
Drug	Excellent	Satisfactory	Fair
Atracurium	7 96.9 (83.8–99.6)	3 83.7 (76.3–92.5)	0
Org NC45	8 97.3 (89.2–99.6)	2 90.3 (86.5–93.3)	0
Pancuronium	7 97.5 (95.5–99.2)	2 93.6 (90.1–96.1)	1 75.9

The potency of atracurium was previously estimated by Payne and Hughes (1981) who found 81% and 98% depression of twitch height with 200 and 300 $\mu g\ kg^{-1}$ respectively. These results are similar to ours (84.9% and 94.5% after 220 and 275 $\mu g\ kg^{-1}$). The absolute and relative potencies of Org NC45 and pancuronium in our study were comparable to previous reports (Agoston et al., 1980; Crul and Booij, 1980; Krieg, Hendrickx and Crul, 1981). Fahey and colleagues (1981) found Org NC45 to be about 1.5 times more potent than pancuronium under halothane anaesthesia. After prior administration of suxamethonium, Krieg, Crul and Booij (1980) found this potency ratio to be about 1.7. The estimated ED$_{95}$ of pancuronium in our study was similar to their finding (62.2 $\mu g\ kg^{-1}$), but slightly greater than that reported by Donlon and colleagues (1980) (55 $\mu g\ kg^{-1}$, using 0.25 Hz nerve stimulation). The dose–response curve for pancuronium was insignificantly steeper than for Org NC45, which is in aggreement with previous reports (Crul and Booij, 1980; Krieg, Crul and Booij, 1980).

The three drugs provided equal and generally good intubating conditions after administration of approximately equipotent doses producing about 95% twitch depression. Donlon, Ali and Savarese (1974) reported on overall adequate intubating conditions at this response level, using 0.25 Hz nerve stimulation. The best conditions for endotracheal intubations were observed in those patients with the most marked depression of twitch response. Statistical comparison between twitch responses at different intubating conditions is omitted because sample sizes are small and unevenly distributed. Krieg and co-workers (1980), using Org NC45, reported no significant difference in twitch height between patients with different intubating conditions.

Evaluation of cardiovascular effects of the drugs *per se* cannot be made without a control group. In previous investigations both atracurium and Org NC45 were reported to be devoid of cardiovascular side-effects (Krieg, Crul and Booij, 1980; Payne and Hughes, 1981). Our study showed little difference between these two drugs, although there was a 6.8% greater decrease in heart rate after Org NC45 which could, however, be attributed to a 10% higher initial value. Our finding that pancuronium produced a significantly higher arterial pressure than atracurium and significantly more rapid heart rate than both atracurium and Org NC45, is consistent with previous reports of stable or increased arterial pressure and heart rate after the injection of pancuronium (Kelman and Kennedy, 1971; Coleman et al., 1972; Harrison, 1972).

In conclusion, Org NC45 was found to be five times more potent than atracurium and slightly more potent than pancuronium. The dose–response curves yielded nearly parallel, straight lines on a log-probit diagram. The relative potencies at ED_{95} are therefore likely to be valid also for the larger doses commonly used in anaesthesia. Equally good intubating conditions at 95% twitch depression indicate that the clinical dose range for the drugs will correspond to their estimated potency ratio. The lack of chronotropic and hypertensive effects of atracurium and Org NC45 may make the drugs acceptable in relatively greater doses than pancuronium.

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RELATION DOSE–REPONSE DE L'ATRACURIUM, DE L'ORG NC45 ET DU PANCURONIUM

RESUME

Nous avons déterminé les puissances de l'atracurium, de l'Org NC45 et du pancuronium en utilisant les courbes dose–réponse cumulatives. Les doses efficaces entraînant une dépression de 95% du twitch étaient 279 $\mu g\,kg^{-1}$, 56 $\mu g\,kg^{-1}$ et 69 $\mu g\,kg^{-1}$ respectivement, la puissance relative étant 1:5,0:4,3. Les courbes dose–réponse calculées "log-probit" ont fait apparaître la pente la plus raide pour le pancuronium, bien que les pentes ne s'écartent pas significativement de parallèles. Les trois agents ont fourni des conditions d'intubation équivalentes et bonnes dans l'ensemble à environ 95% de dépression du twitch. La pression artérielle et la fréquence cardiaque étaient plus élevées avec le pancuronium qu'avec l'atracurium et l'Org NC45.

DOSIS-WIRKUNGSBEZIEHUNG FÜR ATRAKURIUM, ORG NC45 UND PANCURONIUM

ZUSAMMENFASSUNG

Die Wirkungen von Atrakurium, Org NC45 und Pancuronium wurden bestimmt, indem Dosis-Wirkungs-Kurven mit kumulierenden Dosen verwendet wurden. Die Dosen, die zu 95% die Kontraktilität unterdrückten, waren 279 $\mu g\,kg^{-1}$, 56 $\mu g\,kg^{-1}$ und 64 $\mu g\,kg^{-1}$ wie in obiger Reihefolge, wobei die relativen Wirkungen sich wie 1:5:4,3, verhielten. Die berechneten logarithmischen Dosis-Wirkungs-Kurven zeigten den steilsten Verlauf für Pancuronium obwohl die abfallenden Kurven sich nicht signifikant von den parallelen Kurven unterschieden. Die drei Mittel bewirkten gleiche und in allgemeinen gute Intubationsbedingungen bei ungefähr 95%-iger Unterdrückung der Kontraktilität. Bei Pancuronium beobachteten wir einen höheren arteriellen Blutdruck und eine höhere Pulsfrequenz als bei Atrakurium und Org NC45.

RELACION DE DOSIS–RESPUESTA PARA EL ATRACURIO, EL ORG NC45 Y EL PANCURONIO

SUMARIO

Se determinaron las potencias del atracurio, del Org NC 45 y del pancuronio haciendo uso de curvas acumulativas de dosis–respuesta. Las dosis efectivas que produjeron una depresión espasmódica del 95% fueron de 279 $\mu g\,kg^{-1}$, 56 $\mu g\,kg^{-1}$ y 64 $\mu g\,kg^{-1}$ respectivamente; siendo la potencia relativa de 1:5,0:4,3. Las curvas logarítmicas de dosis–respuesta mostraron las mayores pendientes para el pancuronio, aunque todas ellas fueron paralelas sin cambios significativos. Las tres drogas presentaron condiciones de intubación iguales y generalmente buenas a una depresión espasmósdica de aproximádamente el 95%. Se apreció un mayor ritmo cardiaco y presión arterial con el pancuronio que con el atracurio y el Org NC45.

Br. J. Anaesth. (1982), 54, 653

AGE-DEPENDENT DOSE–RESPONSE RELATIONSHIP OF ORG NC45 IN ANAESTHETIZED PATIENTS

A. D'HOLLANDER, F. MASSAUX, M. NEVELSTEEN AND S. AGOSTON

SUMMARY

The effects of age on the dose of Org NC45 were studied in 24 healthy, anaesthetized patients using an on-demand infusion of the drug which produced a stable twitch height of 10% of its initial value. The patients were allocated as follows: group I = age < 40 yr; group II = 40–60 yr and group III = age > 60 yr. A steady-state dose measured every 10 min, was achieved in all the patients 30 min after the start of the administration of Org NC45. Significant decreases of steady-state dosage requirement ($P = 0.01$) and rate of recovery from blockade ($P < 0.01$) were observed between group III and the other two groups.

Org NC45, a 16-monoquaternary derivative of pancuronium, has been demonstrated experimentally and clinically to be a non-depolarizing agent of short duration of action with minimal cumulative effects following repeated administration (Agoston et al., 1980; Durant, Houwertjes and Crul, 1980; Fahey et al., 1980; Krieg, Crul and Booij, 1980). These properties suggest that a continuous infusion (Miller and Eger, 1976) of the drug, in appropriate dose, could produce stable neuromuscular blockade. However, since previous data demonstrated that age alters the pharmacokinetics (McLeod, Hull and Watson, 1979) and the pharmacodynamics (Duvaldestin et al., 1981) of pancuronium, the aims of this investigation were first, to establish the dose of Org NC45 required to maintain a steady state neuromuscular blockade in relation to age; second, to investigate any cumulative effects in older patients and third, to evaluate the effects of age on the rate of recovery from blockade on discontinuation of the infusion.

PATIENTS AND METHODS

Twenty-four adult patients undergoing elective surgery were studied with informed consent. None of the patients had any clinical or biochemical evidence of hepatic or renal damage. These patients were divided into three groups according to their age: group I ($n = 8$), age less than 40 yr; group II ($n = 8$), age between 40 and 60 yr and group III ($n = 8$), age more than 60 yr. One hour before anaesthesia, all patients received diazepam 10 mg by mouth. Anaesthesia was induced with methohexitone 1 mg kg^{-1} and fentanyl 5 μg kg^{-1} i.v. Following the onset of unconsciousness, ventilation of the lungs was controlled manually (semi-open circuit, 50% oxygen in nitrous oxide) until intubation of the trachea, which was performed after the administration of Org NC45. Thereafter, ventilation was controlled mechanically (semi-closed circuit, 33% oxygen in nitrous oxide) until the end of the surgical procedure. Ventilation was adjusted to produce normocapnia (end-tidal carbon dioxide about 5.0 ± 0.1% measured with a Datascope 500 carbon dioxide analyser; arterial $P\text{CO}_2$ between 4.79 kPa and 5.59 kPa). Supplementary doses of fentanyl were administered if there was clinical evidence of inadequate analgesia. Heat-loss from the body core and the exposed left arm was decreased by the use of a warming mattress (rectal temperature 37 °C).

A force displacement transducer (UC3 cell Statham), fitted with tension attenuator (UL4–20, Statham) and incorporated in a hand grip, was secured with adhesive tape in the left hand of the patient to measure the isometric contraction of the adductor pollicis. Following the induction of anaesthesia two 25-gauge thin-walled needles were placed subcutaneously near the ulnar nerve at the wrist and mechanical activity was induced in the adductor pollicis by square-wave pulses of 0.2 ms duration and supramaximal intensity, delivered at 0.1 Hz from a Grass S88 stimulator. The resulting analog signals were amplified and registered on a polygraph recorder. When a consistent control tension was achieved, after a few minutes, a bolus injection of Org NC45 0.07 mg kg^{-1} was administered (at time

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t_0). Tracheal intubation was performed at the minimum twitch height (TH) value. Thereafter, TH was maintained constant at 10% of its baseline reading by manually adjusting the flow of a Harvard syringe containing Org NC45 160 $\mu g\ ml^{-1}$ in physiological saline. The amount of Org NC45 required was calculated every 10 min by measuring the displacement of the piston. This infusion was continued for at least 90 min or for as long as required by the surgical procedure.

The pharmacodynamic parameters measured were:

(1) The time elapsed between the end of the administration of Org NC45 and recovery to 25% of original twitch height (TH 25): TH 10–25 period.

(2) The time for the recovery from TH 25 to TH 75%: TH 25–75 period or recovery rate.

The statistical analysis of the results was performed using unpaired Wilcoxon rank sum test, two-way variance and linear regression analyses. Significance was assigned at a level of 5% or less.

RESULTS

Initially, the amount of Org NC45 required decreased progressively, becoming relatively constant around 30 min after administration (fig. 1). Although there were individual variations in this steady-state dose requirement (SSDR) which ranged from 889 to 4469 $\mu g\ m^{-2}\ h^{-1}$, this variable was related to the age of the patients (mean ± SEM): group I, 3046 ± 438 $\mu g\ m^{-2}\ h^{-1}$; group II, 2448 ± 280 $\mu g\ m^{-2}\ h^{-1}$; group III, 1775 ± 213 $\mu g\ m^{-2}\ h^{-1}$ (table I).

The patients in group III showed significantly (Wilcoxon rank sum test) lower SSDR ($P < 0.05$), than the patients in groups I and II. There was no significant difference between these two last groups.

Cumulation of Org NC45 was not observed during the on-demand infusion; there were no significant (two-way analysis of variance) time-related decreases in the relative amounts of Org NC45 required in these patients during the 60 min which followed the onset of the steady-state (fig. 2).

The periods TH 10–TH 25 and TH 25–75 were prolonged significantly in the patients in group III compared with those in groups I and II ($P < 0.05$ and $P < 0.01$, respectively) (table I). Using pooled results to correlate age with SSDR and age with the rate of recovery the following linear regressions were obtained:

Org NC45 ($\mu g\ m^{-2}\ h^{-1}$) $= -27.31 \times$ age (yr) $+ 3803$; $r = -0.51$, $P = 0.01$.

TH 25–75 (min) $= 0.557 \times$ age (yr) $+ 0.189$; $r = 0.58$, $P < 0.01$.

DISCUSSION

The dose of non-depolarizing neuromuscular blocking drug, administered by an on-demand infusion method, required to produce a steady-state blockade rapidly becomes relatively constant (Miller and

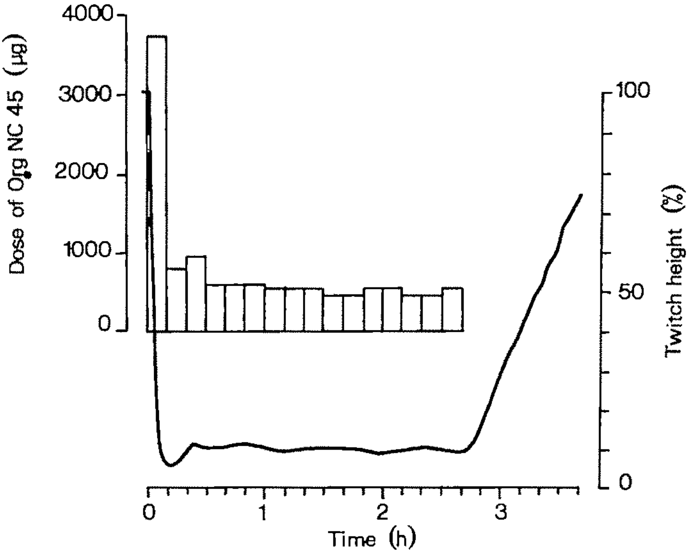

FIG. 1. The dose of Org NC45 measured every 10 min illustrated with the twitch height (solid line) in one patient from group III.

TABLE I. *The dose of Org NC 45 required to produce a steady state blockade and the rates of recovery (TH 10–25 and TH 25–75) in the different age groups (mean ± SEM; range in parentheses). *P < 0.05; **P < 0.01, Wilcoxon unpaired rank sum test*

	Group I (age < 40 yr)	Group II (age 40–60 yr)	Group III (age > 60 yr)
Age (yr)	28 ± 2 (18–36)	54 ± 3 (40–60)	69 ± 3 (63–85)
Org NC 45 SSDR ($\mu g\, m^{-2} h^{-1}$)	2791 ± 434 (1348–4469)	2702 ± 325 (1546–3973)	1775 ± 213 (889–2816)
		*	
	n.s.		*
TH 10–25 (min)	8.44 ± 1.16 (4–14)	9.18 ± 1.40 (5–14)	14.70 ± 182 (7.8–17.8)
		*	
			*
	n.s.		
TH 25–75 (min)	16.24 ± 4 (3–37.1)	21.88 ± 2.2 (16–33)	44.94 ± 6.91 (27.5–82)
		**	
			**
	n.s.		

Eger, 1976). As a given twitch height is obtained in the presence of a particular plasma concentration of drug (Shanks, Somogyi and Triggs, 1978; Sheiner et al., 1979), the amount of the blocking drug administered is related to the amount of the drug which is cleared from the plasma by distribution and elimination. In the present study this constant rate of administration was achieved within 30 min, a shorter period than those reported for tubocuraine and pancuronium (Miller and Eger, 1976). This rapid characterization of the dose of Org NC 45 required is probably related to the pharmacokinetic properties of the drug and, in particular, to its rapid distribution phase as compared with that of other competitive neuromuscular blocking agents (Van Der Veen and Bencini, 1980; Ramzam et al., 1981). With the on-demand method, the absence of any major change in the dose required 30 min after the initial administration would appear to support evidence of its lack of cumulation obtained previously by demonstrating that there was no prolongation of mechanical depression following repeated injections (Fahey et al., 1980).

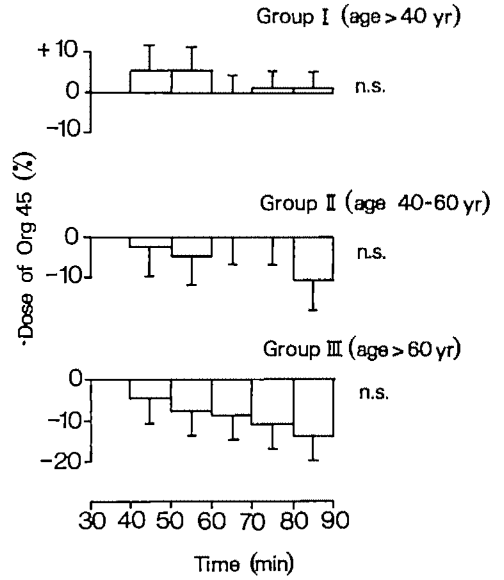

FIG. 2. The dose of Org NC 45 required to produce a steady-state 90% depression of twitch height measured at 10-min intervals from 30 to 90 min, and expressed as a percentage of the dose observed for the $t + 30$–$t + 40$-min periods (mean ± SEM).

The present results show clearly that ageing can affect the absolute SSDR of Org NC 45 since this index was significantly less for patients older than 60 years of age when compared with younger subjects. In addition, once the infusion of Org NC 45 was stopped, the rate of recovery of the mechanical response was prolonged in the patients in group III. Thus, both SSDR and rate of recovery correlated with age (linear regression analyes are presented in the results section). These age-related differences, which are manifest after 60 years of age, are the result of progressive decreases in organ function: cardiac output (Brandfonbrener, Landowne and Shock, 1955), hepatic and renal function (Davies and Shock, 1950; Calloway and Merill, 1965) which decrease the elimination or biotransformation of the drug, or both. On the other hand, these effects may be the result of progressive physico–chemical changes which can affect the pharmacodynamic drug–time relationship as suggested by Triggs and Nation (1975). In the absence of measurements of the plasma concentrations of Org NC45 in the present study we were unable to test the two hypotheses separately. Nevertheless, as the relationship between plasma concentration and mechanical effects of pancuronium (a congeneric drug) is not markedly affected by ageing (Duvaldestin et al., 1981) one may reasonably believe that the decrease in the absolute SSDR for Org NC45 indicates that the elimination or biotransformation, or both, of this molecule are decreased in older patients. A decrease in the plasma clearance of Org NC45 in older patients, as previously reported for pancuronium (McLeod, Hull and Watson, 1979; Duvaldestin et al., 1981), explains partly or totally the delay in the recovery of the twitch height in these patients since rate of recovery of twitch height and the rate at which the plasma concentration decreases are generally correlated in the TH25–75 interval (Hull et al., 1978; Shanks, Somogyi and Triggs, 1979; d'Hollander et al., 1981).

In conclusion, this study shows that the dose of Org NC45 and the rate of recovery of twitch height are age-dependent and serves to emphasize the need to decrease the maintenance dose of competitive neuromuscular blocking drugs, the elimination of which is dependent on renal and hepatic function in elderly patients.

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ETUDE EN FONCTION DE L'AGE DE LA RELATION DOSE–REPONSE DE L'ORG NC 45 CHEZ DES PATIENTS ANESTHESIES

RESUME

Les effets de l'âge sur la dose de l'Org NC45 ont été étudiés chez 24 patients adultes anesthésiés en bonne santé, en utilisant une perfusion à la demande du produit pour produire une hauteur stable du twitch à 10% de sa valeur initiale. Les patients ont été classés de la façon suivante: groupe I: âge <40 ans; groupe II: âge

de 40–60 ans et groupe III: âge > 60 ans. Une posologie d'équilibre, mesurée toutes les 10 min, a été obtenue chez tous les patients 30 min après le début de l'administration de l'Org NC 45. Des diminutions significatives des posologies nécessaires à l'équilibre ($P<0,05$) et de la vitesse de récupération du bloc ($P<0,01$) ont été observées entre le groupe III et les deux autres groupes.

ALTERABHÄNGIGE DOSIS-ANTWORT-BEZIEHUNG VON ORG NC 45 BEI NARKOTISIERTEN PATIENTEN

ZUSAMMENFASSUNG

Es wurden die Auswirkungen des Lebensalters auf die Dosis des Org NC 45 bei 24 gesunden erwachsenen Patienten in Narkose studiert, in dem bei Bedarf über eine Infusion das Mittel gegeben wurde, das eine stabile Höhe von 10% der Anfangskontraktilität herstellte. Die Patienten waren wie folgt eingeteilt: Gruppe 1: Alter unter 40 Jahre; Gruppe 2: 40–60 Jahre und Gruppe 3: Alter über 60 Jahre. Eine Dosis die den Gleichgewichtzustand herstellte, und alle 10 Minuten gemessen wurde war bei allen Patienten 30 min nach Beginn der Infusion von Org NC 45 erreicht. Eine signifikante Abnahme sowohl der Dosen, die notwendig waren um den Gleichgewichtzustand zu halten ($P<0,05$) als auch der Erholungszeit nach der Blockade ($P<0,01$) war zwischen Gruppe 3 und den anderen Gruppen zu beobachten.

INFLUENCIA DE LA EDAD Y DE LA DOSIS EN EL EFECTO DEL ORG NC 45 EN PACIENTES ANESTESIADOS

SUMARIO

Se estudió la influencia de la edad en la dosis del Org NC 45 en 24 pacientes adultos, sanos y anestesiados, haciendo uso de una infusión de la droga que se administraba bajo demanda y que produjo un máximo de espasmo del 10% con relación a su valor inicial. A los pacientes se les asignó como sigue: grupo I = edad < 40 años; grupo II = 40–60 años y grupo III = edad > 60 años. Se logró una dosis de régimen estacionario cada 10 minutos, en todos los pacientes, a los 30 minutos de la administración de Org NC 45. Entre el grupo III y los otros dos grupos se observó una disminución significativa de la dosis de régimen estacionario necesaria ($P<0,05$) y del régimen de recuperación del estado de bloqueo ($P<0,01$).

Br. J. Anaesth. (1982), 54, 659

ELECTROENCEPHALOGRAPHIC AND BEHAVIOURAL EFFECTS OF ENFLURANE AND HALOTHANE ANAESTHESIA IN THE CAT

G. M. BASSELL, B. F. CULLEN, M. D. FAIRCHILD AND J. A. KUSSKE

SUMMARY

The effects of enflurane and halothane on the electroencephalogram (e.e.g.) were studied in 10 cats. Animals underwent at least 2 MAC-hours of anaesthesia with either agent, and the e.e.g. was monitored continuously. Arterial blood-gas tensions were maintained within normal limits. In addition, e.e.g. and behaviour were monitored during the period following anaesthesia, at fixed intervals, for 4 weeks. Despite the production of the central stimulatory effects of enflurane during anaesthesia, no animal demonstrated any central nervous system sequelae on any occasion following the anaesthetic.

The introduction of enflurane into clinical anaesthesia was followed by several reports detailing unexpected central nervous system activity associated with its use. These effects ranged from motor hyperactivity to frank electroencephalogram (e.e.g.) seizure patterns, and were made worse by hypocarbia or increased depth of anaesthesia, or both (Neigh, Garman and Harp, 1971). Although the existence of enflurane-induced central nervous system stimulation is not disputed (Virtue et al., 1966; Joas, Stevens and Eger, 1972), its clinical significance is unclear. In fact, there is evidence that the anaesthetic can act both to inhibit as well as to excite epileptic foci (Leibowitz, Blitt and Dillon, 1972; Gallagher, Galindo and Richey, 1978).

Unexplained seizures have been reported in two patients, 6 and 8 days *after* an enflurane anaesthetic (Ohm et al., 1975) and, more recently, Kruczek and his associates (1980) reported a solitary convulsion occurring 1 h after anaesthesia. In both reports, the patients had not experienced any previous seizures. In cats, both e.e.g. and behavioural abnormalities have been demonstrated following the administration of enflurane (Julien and Kavan, 1972; Kavan, Julien and Lucero, 1972). However, since these accounts did not include control of the many variables that can affect the central nervous system during and after anaesthesia, we undertook the present study in animals so that the anaesthetic and post-anaesthetic effects of enflurane alone could be clarified, and compared with those of halothane.

METHODS

Ten adult female cats, weighing between 2.7 and 5.28 kg (mean 3.58 kg), and anaesthetized with sodium pentobarbitone, had bipolar 40-gauge stainless steel electrodes implanted in the prepyriform cortex, septum, ventral hippocampus, dorsal hippocampus, basolateral amygdala and lateral geniculate body. In addition, electrical activity from the sensory-motor and occipital (striate) cortices was recorded from small stainless steel screws embedded in, but not penetrating the calvaria. The prepyriform cortical electrode was implanted by observing the characteristics of potentials evoked in the target site by electrical stimulation of afferent pathways (Fairchild, Jenden and Mickey, 1975). Electrodes in subcortical structures were positioned using standard stereotaxic procedures. After implantation, all electrode leads were soldered to a 20-pin plug which was permanently fixed to the skull with acrylic plastic. The animals were allowed to recover for at least 1 month before starting the series of experiments with enflurane and halothane.

On the day of the experiment, the unpremedicated, fasting cat was weighed, connected to the e.e.g. input circuit by a low-noise flexible cable, and placed in an observation area for a 5-min recording of awake electrical activity. At the conclusion of this control period, the animal was placed on an operating table and restrained gently. Anaesthesia was induced, using a mask, by the inhalation in oxygen of the agent being studied. When a suitable plane of anaesthesia had been achieved, the trachea was intubated and a pneumograph was attached to monitor

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respiratory rate. A femoral arterial catheter was inserted for the continuous monitoring of arterial pressure and to permit blood sampling for blood-gas and pH determinations. A heating blanket and rectal thermistor permitted maintenance of normal body temperature.

Anaesthesia was administered for 2 h using a Mapleson E anaesthetic system. Because of the variation in inspired anaesthetic concentrations necessary to prevent responses to frequent tail clamping, the MAC-hours of anaesthesia administered varied from 2.2 to 6.2 for halothane, and from 4.8 to 8.1 for enflurane (table I). Ventilation was augmented where necessary to maintain arterial carbon dioxide tension at less than 6.7 kPa. Arterial pressure remained greater than 40 mm Hg in all animals (table I). Halothane or enflurane was delivered in oxygen by a Vernitrol vaporizer which was calibrated by gas chromatography. No drug, other than the anaesthetics under study, was administered during the 3 months of experimentation.

Inspired concentrations of each anaesthetic were measured by gas chromatography. E.e.g., arterial pressure, and respiratory rate were recorded continuously during the experiment and stored on analog tape for subsequent analysis.

At the conclusion of each investigation, the anaesthetic was discontinued and the animal allowed to awaken with the endotracheal tube *in situ*. When the cat had recovered consciousness sufficiently, as assessed both clinically and by e.e.g., the trachea was extubated and the animal was disconnected from the e.e.g. cable. At this stage, the cat was observed closely for early behavioural abnormalities such as excitability or unusual movements.

Ten animals were randomly assigned to two groups of five. Cats in the first group received halothane during the initial set of experiments and enflurane during the second. The order was reversed for the subsequent series. Thus all 10 cats received both anaesthetics and served as their own controls. The two groups of experiments were performed over a 3-month period, with 40–46 days separating the administration of the two anaesthetics. After each experiment, the cat's e.e.g. and behaviour were monitored for 30 min at 24, 48, and 96 h, thence bi-weekly for an additional 4 weeks. The follow-up e.e.g. were visually inspected to identify unusual alterations in frequency spectra and to detect the presence of abnormal sharp wave activity. Behavioural observations were recorded following each 1-min period.

RESULTS

Enflurane and halothane were both associated with the development of a "fast rhythm" in the prepyriform cortex and amygdala which ranged between 12 and 50 Hz (fig. 1). This unusual finding appeared to be dose-related in individual cats and could be produced by varying the inspired concentration. Although the rhythm occurred most commonly during induction, it also appeared at deeper planes of anaesthesia. Halothane produced the phenomenon more often, but with enflurane it could easily have been masked by the synchronous spiking and periods of postictal silence present in the e.e.g. at surgical planes of anaesthesia.

Induction with enflurane was characterized by the appearance of this "fast rhythm" in the prepyriform cortex and amygdala, while at the same

TABLE I. *Femoral arterial pressure, Po_2, Pco_2 and pH presented as the range of measurements obtained during the experiments. The MAC-hours of anaesthesia are given for each type of volatile anaesthetic. N/A = data not available because of equipment malfunction*

Cat	MAC-hours of anaesthesia		Femoral arterial pressure range (mm Hg)		Pa_{O_2} range (kPa)		Pa_{CO_2} range (kPa)		pH range (unit)	
No.	Halothane	Enflurane	Halothane	Enflurane	Halothane	Enflurane	Halothane	Enflurane	Halothane	Enflurane
1	6.2	4.8	58–66	58–64	75–78	68–75	3.4–4.9	3.2–4.9	7.42–7.53	7.35–7.45
2	3.7	5.8	54–76	78–95	60–69	58–61	4.6–5.5	4.9–5.6	7.26–7.33	7.42–7.47
3	3.4	6.0	60–86	50–64	69–72	68–70	3.8–4.4	5.2–5.9	7.25–7.31	7.36–7.40
4	4.7	6.5	44–52	80–84	51–70	52–74	3.8–4.5	3.7–4.5	7.29–7.38	7.29–7.34
5	4.4	7.1	76–82	48–70	57–71	71–73	3.6–5.4	3.3–4.7	7.25–7.33	7.35–7.41
6	3.8	7.8	61–80	N/A	53–58	N/A	4.4–5.6	N/A	7.27–7.35	N/A
7	2.2	8.1	N/A	47–60	58–65	52–60	3.7–5.0	3.6–5.2	7.29–7.38	7.27–7.43
8	5.1	7.4	47–59	41–58	67–69	64–67	4.3–5.3	3.4–3.9	7.27–7.30	7.31–7.42
9	2.5	7.5	45–52	52–74	70–77	53–63	3.6–5.7	3.6–4.5	7.26–7.38	7.27–7.35
10	3.4	7.0	41–64	64–74	50–77	73–78	3.7–5.5	3.5–4.7	7.23–7.45	7.24–7.34

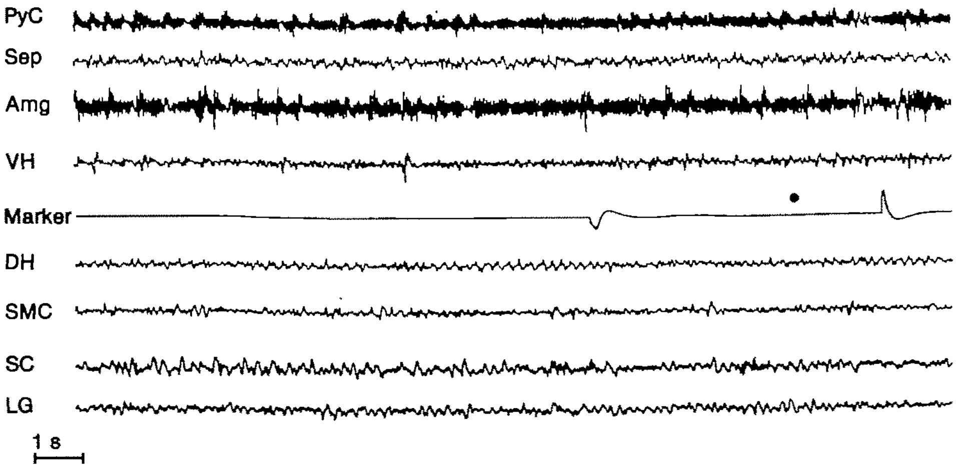

FIG. 1. The fast rhythm seen in the prepyriform cortex (PyC) and basolateral amygdala (Amg) occurred with both enflurane and halothane anaesthesia but, as here, more often with the latter. Sep = septal area; VH = ventral hippocampus; DH = dorsal hippocampus; SMC = sensory motor cortex; SC = striate cortex; LG = lateral geniculate.

time slow waves began to appear in other brain areas. Spiking activity followed in quick succession in all zones, first infrequently, then more often until each lead was recording numerous spikes. Gradually, the spiking activity became synchronous throughout the brain, and brief episodes of silence appeared. As the cat reached a light surgical plane of anaesthesia, groups or trains of spikes, with progressively longer periods of silence, gave way to very large amplitude single or double synchronous spikes, and motor phenomena such as limb clonus occurred. At this stage, grand mal convulsions could be elicited by repetitive peripheral stimuli such as handclapping near the animal's ear or flicking the ear itself (fig. 2). Occasionally, hippocampal structures appeared resistant to the epileptogenic action of enflurane. This is in direct contrast to the usual behaviour of the hippocampus which normally has a relatively low convulsive threshold.

During induction with halothane, the "fast rhythm" was evident in the prepyriform cortex and amygdala. Soon thereafter, slow wave activity became progressively dominant in all areas monitored. Both the dorsal and ventral hippocampi developed the type of large amplitude sharp waves which are usually detected in the unanaesthetized sleeping cat. These were probably unmasked by halothane as a result of a decrease in the fast-frequency components of the e.e.g. As anaesthesia was deepened, changes were detected in the occurrence and frequency of this "fast rhythm" in those cases where it did occur. As halothane anaesthesia progressed, there was a gradual, overall decrease in e.e.g. amplitude which, although evident in all animals, was particularly obvious in three.

During the observation period following anaesthesia, no cat exhibited any abnormality in e.e.g. or behaviour. The animals were normal not only during the planned periods of assessment, but also during additional "chance" observations.

DISCUSSION

This cross-over study in cats with halothane and enflurane failed to demonstrate any e.e.g. abnormalities following the administration of enflurane such as those previously reported in cats by Julien and Kavan (1972). In their experiments, administration of enflurane for 30 min resulted in high voltage spikes in the cortex and thalamic nuclei plus behavioural abnormalities for up to 16 days following the anaesthetic. This study has been extensively quoted as evidence for long-term, enflurane-induced central nervous system abnormalities.

There were important differences in methodology between our study and that of Julien and Kavan. First, we administered enflurane in 100% oxygen, whereas they used a 2:1 mixture of air and oxygen. Second, the cats in our experiments had the trachea intubated while the animals used by Julien and Kavan were anaesthetized via masks. Finally, in our animals, arterial pressure and blood-gas tensions were maintained within fixed limits throughout.

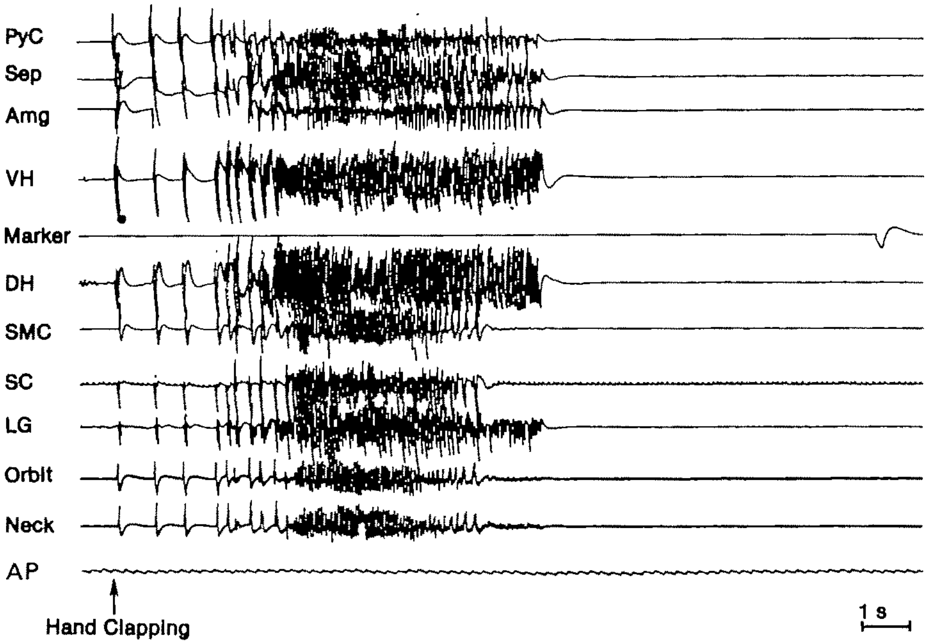

FIG. 2. Production of grand mal seizures in the enflurane-anaesthetized cat by repetitive hand clapping near the animal's ear. In this cat, the seizure period of approximately 10 s was followed by electrical silence lasting more than 20 s. AP = femoral arterial pressure; other abbreviations as figure 1.

Although speculative, it is possible that the delayed e.e.g. and behavioural abnormalities observed by Julien and Kavan could have resulted from inadvertent cerebral hypoxia during the anaesthetic, hypoventilation while breathing a lower inspired oxygen concentration, or undocumented hypotension.

When Burchiel and co-workers (1977) administered enflurane anaesthesia to 12 human volunteers for 9.6 MAC-hours, frank e.e.g. and motor seizure activity was apparent during narcosis and diffuse slowing of the e.e.g.—but no epileptiform activity—persisted for 6–30 days in the period following anaesthesia. The inability to demonstrate epileptiform activity after enflurane anaesthesia in human volunteers does not, of course, exclude the possibility that such activity could have been observed had implanted depth electrodes been utilized or a large group of volunteers studied.

The repeated association of enflurane with the occurrence of epileptiform e.e.g. activity *during* anaesthesia is at variance with the theory that all anaesthetics act by global depression of the central nervous system. In fact, the central effects of enflurane classify it, together with chloralose and gammahydroxybutyrate, as a stimulant anaesthetic. When the latter two agents are given to animals, loss of consciousness coincides with the appearance of an epileptiform pattern on the e.e.g. Rather than depressing neural activity, the stimulant anaesthetics may inhibit control systems (Killam, 1968), or may alter circulation of activity through various neuronal networks so that a hypersynchronized state exists (Verzeano, 1972).

We noted no e.e.g. or behavioural abnormalities following halothane anaesthesia. This lack of central nervous system effect after halothane is in agreement with the observations made by Kavan, Julien and Lucero (1972), when they anaesthetized cats with halothane, methoxyflurane and diethyl ether.

In conclusion, we have been unable to document any e.e.g. or behavioural abnormalities following the administration of enflurane or halothane to cats. We believe that, if seizure activity occurs after an enflurane anaesthetic, other precipitating factors such as hypoxia should be considered.

ACKNOWLEDGEMENTS

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EFFETS ELECTRO-ENCEPHALOGRAPHIQUES ET COMPORTEMENTAUX DE L'ANESTHESIE A L'ENFLURANE ET A L'HALOTHANE CHEZ LE CHAT

RESUME

Nous avons étudié les effets de l'enflurane et de l'halothane sur l'électro-encéphalogramme (e.e.g.) de 10 chats. Les animaux ont été soumis à au moins 2 MAC-heures d'anesthésie avec l'un ou l'autre agent, et l'e.e.g. a été surveillé de façon continue. Les valeurs des gaz du sang artériel ont été maintenues dans les limites de la normale. De surcroît, l'e.e.g. et le comportement ont été surveillés pendant la période suivant l'anesthésie, à intervalles réguliers pendant 4 semaines. Malgré l'apparition des effets stimulateurs centraux de l'enflurane au cours de l'anesthésie, aucun animal n'a manifesté de séquelles au niveau du système nerveux central, à quelque occasion que ce soit après l'anesthésie.

AUSWIRKUNGEN VON ENFLURANE UND HALOTHANNARKOSEN AUF E.E.G. UND VERHALTEN VON KATZEN

ZUSAMMENFASSUNG

Die Auswirkungen von Enflurane und Halothan auf das E.E.G. wurden bei 10 Katzen untersucht. Die Tieren mussten sich einer mindestens 2stündigen Narkose unterzehen wobei das E.E.G. kontinuierlich aufgezeichnet wurde. Die arteriellen Blutgasspannungen hielt mann innerhalb der normalen Grenzen. Zusätzlich wurden E.E.G. und Verhalten nach der Narkose vier Wochen lang in bestimmten Abstände registriert. Trotz der zentral stimulierenden Wirkung von Enflurane während der Narkose zeigte kein Tier irgendwelche zentralnervösen Erscheinungen nach der Narkose.

EFECTOS SOBRE COMPORTAMIENTO Y ELECTROENCEFALOGRAFIA DE LA ANESTESIA POR ENFLURANO Y HALOTANO EN EL GATO

SUMARIO

Se estudiaron en 10 gatos los efectos del enflurano y del halotano sobre el encefalograma (e.e.g.). Los animales fueron sometidos a por lo menos 2 horas-MAC de anestesia con cualquiera de los dos agentes, y se verifocó el e.e.g. continuamente. Se mantuvieron las tensiones de gasos del sangre arterial dentro de limites normales. Además, se verificaron el comportamiento y el e.e.g. durante el periodo que siguió la anestesia a intervalos fijos durante 4 semanas. A pesar de la producción de efectos estimuladores centrales del enflurano durante la anestesia, ningún animal demostró secuelas del sistema nervioso central en alguna oportunidad después de la anestesia.

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THE RESPONSE OF CANINE INTRACRANIAL PRESSURE TO SYSTEMIC HYPOTENSION INDUCED WITH NITROGLYCERINE

D. E. R. BURT, A. J. W. VERNIQUET AND J. HOMI

SUMMARY

Changes in intracranial pressure were studied in 18 greyhounds in relation to decreases in systemic arterial pressure produced by nitroglycerine. At normal values of i.c.p. (<12 mm Hg) GTN produced an increase in i.c.p. of 3.1 (±0.6) mm Hg (mean ± SEM). Under conditions of increased i.c.p. (12+ mm Hg) small decreases in mean arterial pressure (m.a.p.) ($<25\%$ control) were associated with an increase of 4.7 (±0.5) mm Hg, whereas larger decreases in m.a.p. ($>25\%$ control) were associated with a decrease of 3.2 (±0.9) mm Hg in i.c.p. In 11 of 19 observations in which a decrease in intracranial pressure had occurred in association with systemic hypotension there was a rebound increase in i.c.p. as m.a.p. was restored. It is suggested that i.c.p. be decreased before this drug is used to produce hypotension during neurosurgery.

In neurosurgical anaesthesia there is a clearly defined role for a safe, easily controlled and effective hypotensive agent. Recent demonstrations of the ability of nitroglycerine (GTN) to produce controlled hypotension (Fahmy, 1978) have led to a growing interest in its use. GTN lacks the toxic metabolites that limit the use of agents such as sodium nitroprusside, does not usually produce rebound hypertension, and is a short-acting, easily controlled drug with a long record of safety in the control of angina. However, in neurosurgical practice the effect of a drug on intracranial pressure (i.c.p.) is of paramount importance. In this respect there is some controversy as to the effects of GTN. Chestnut and colleagues (1978) found no change in i.c.p. with an infusion of nitroglycerine in dogs at increased values of i.c.p., and small increases in pressure when the i.c.p. was normal. Other workers (Rogers et al., 1979; Cottrell et al., 1980; Cottrell, Gupta and Turndorf, 1980) have consistently noted increased i.c.p. when the arterial pressure was decreased with GTN.

The present study was undertaken to evaluate the relationship between decreases in systemic arterial pressure produced by GTN and i.c.p. under normal conditions, and following a decrease of intracranial compliance.

METHODS

Eighteen adult greyhounds weighing between 18 and 30 kg were anaesthetized with a mixture of thiopentone 7–8.5 mg kg^{-1} and pentobarbitone 20 mg kg^{-1}. Anaesthesia was maintained with an infusion of fentanyl 3.3 μg kg^{-1} h^{-1} i.v., and their lungs were ventilated with an air–oxygen mixture from a Beaver Mk 3 ventilator to maintain mild hypocapnoea (Pa_{CO_2} 4.6 ± 0.18 kPa; Pa_{O_2} 18.7 ± 1.22 kPa). Blood-gas analyses were performed using an IL 413 automatic analyser. Oesophageal temperature was measured, and maintained within the range of 37 ± 0.5 °C with space heating and insulating foil. Cannulation of the femoral artery allowed continuous measurement and display of arterial pressure (Bell and Howell 4-327-L221 transducer and Devices 4-channel recorder). Mean arterial pressure (m.a.p.) was obtained by electrical integration. The e.c.g. was recorded from limb leads and changes in heart rate monitored using a Devices Instantaneous Ratemeter 2751. The animals were placed in the "sphinx" position and two temporo–parietal burr holes drilled in the skull. A small saline-filled pressure recording balloon was placed in the extradural space on one side, and a balloon catheter capable of being inflated with a varying volume of water, to

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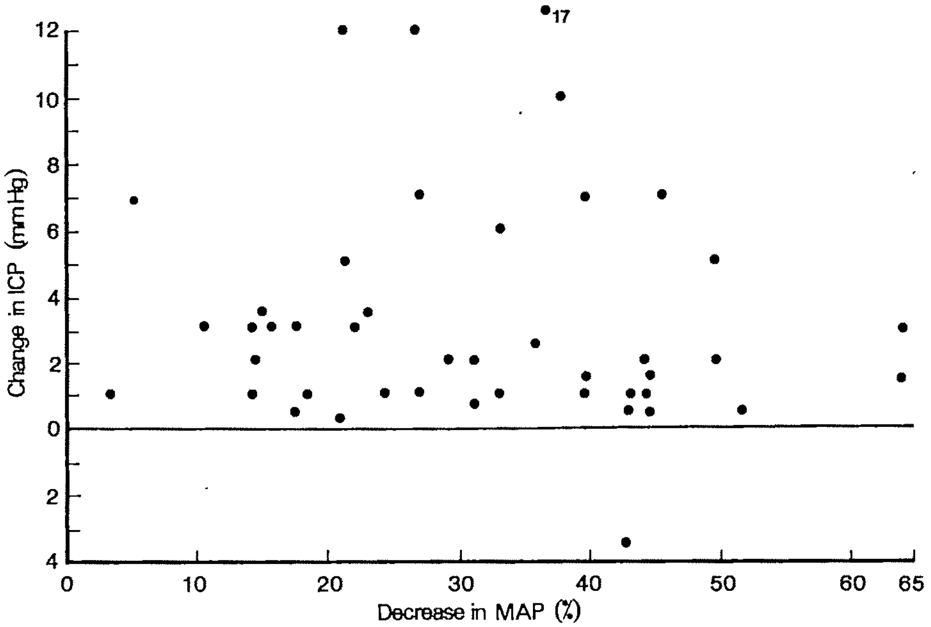

Fig. 1. Individual changes in i.c.p. plotted against percentage changes in m.a.p. following bolus doses of GTN when baseline ICP was less than 12 mm Hg.

simulate a mass lesion, was placed in the extradural space on the opposite side. The burr holes were sealed with bonewax, and the fascia, muscle and skin closed in layers to achieve a water tight seal. The extradural transducer was zeroed at the level of the internal auditory meatus.

The preparation of GTN used (Nitroglycerin Solution—Macarthy) was of 1% strength in 90% alcohol and was diluted in normal saline for injection as required. All injections were made over a period of 10 s through an i.v. cannula in a large peripheral vein. Progressively increasing doses, sufficient to produce appreciable decreases in arterial pressure as based on previous experience, were given to each animal and ranged from 0.05 to 0.2 mg kg^{-1}. Subsequent bolus doses were given when the arterial pressure and i.c.p. had remained stable for 10 min, or under conditions of increased i.c.p. when the rate of compensatory decrease had reached a plateau. Doses were given at normal i.c.p. (less than 12 mm Hg) and after it had been artificially increased above 15 mm Hg. Statistical analysis of the data was performed using Student's *t* test.

RESULTS

Individual observations of the changes in i.c.p. following bolus injections of GTN are shown at normal i.c.p. in figure 1 and after the i.c.p. had been increased artifically in figure 2.

Following the injection of sufficient GTN to pro-

TABLE I. *Changes occurring after bolus doses of GTN in dogs with baseline i.c.p. of less than 12 mm Hg. Mean values ± SEM (range) results from 45 observations. PP = cerebral perfusion pressure; MAP = mean arterial pressure; ICP = intracranial pressure.* **P < 0.001

	Before GTN	After GTN	Change	% Change
MAP (mm Hg)	108.2 ± 3.4 (70–160)	73.6 ± 3.5 (36–130)	34.5 ± 2.7** (10–90)	32.0
ICP (mm Hg)	6.7 ± 0.5 (1–11.5)	9.8 ± 0.9 (1.5–27)	3.1 ± 0.6** (−3.5–17)	46.3
PP (mm Hg)	105.5 ± 3.2 (32–137.5)	63.5 ± 3.3 (26–119)	38.0 ± 2.9** (6–91.5)	37.4

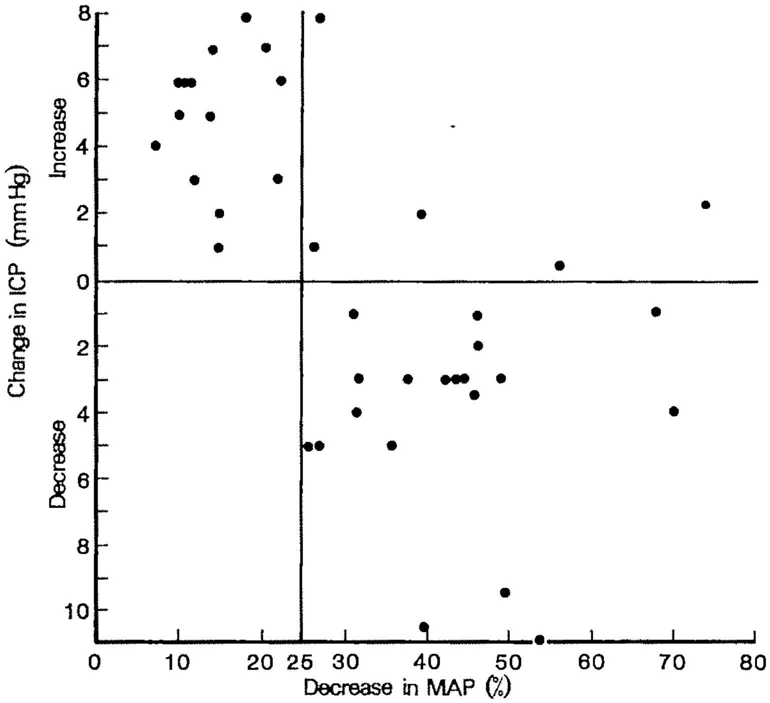

FIG. 2. Individual changes in i.c.p. plotted against percentage changes in m.a.p. following bolus doses of GTN when baseline ICP was greater than 12 mm Hg.

TABLE II. *Changes occurring after bolus doses of GTN in dogs with baseline i.c.p. greater than 12 mm Hg. Mean ± SEM (range).* †$P < 0.005$; ***$P < 0.001$

	Before GTN	After GTN	Change	% Change
Decrease in m.a.p. less than 25% of control (15 observations)				
MAP (mm Hg)	121.3 ± 6.5 (75–145)	104.7 ± 6.8 (55–135)	18.3 ± 1.3† (10–30)	14.9
ICP (mm Hg)	17.1 ± 1.2 (12–28)	21.8 ± 1.2 (15–31)	4.7 ± 0.5† (1–8)	27.5
PP (mm Hg)	106.1 ± 6.9 (61–131)	82.7 ± 6.9 (39–117)	23.3 ± 1.5† (14–37)	23.6
Decrease in m.a.p. greater than 25% of control (23 observations)				
MAP (mm Hg)	99.9 ± 4.0 (65–145)	58.3 ± 4.3 (20–90)	41.6 ± 1.7† (30–55)	41.6
ICP (mm Hg)	18.1 ± 1.5 (12–35)	14.9 ± 1.7 (0–30)	−3.2 ± 0.9*** (+8 to −12)	17.7
PP (mm Hg)	81.8 ± 3.8 (49–130)	43.4 ± 3.6 (8.5–78)	38.4 ± 1.9† (23–54)	48.7

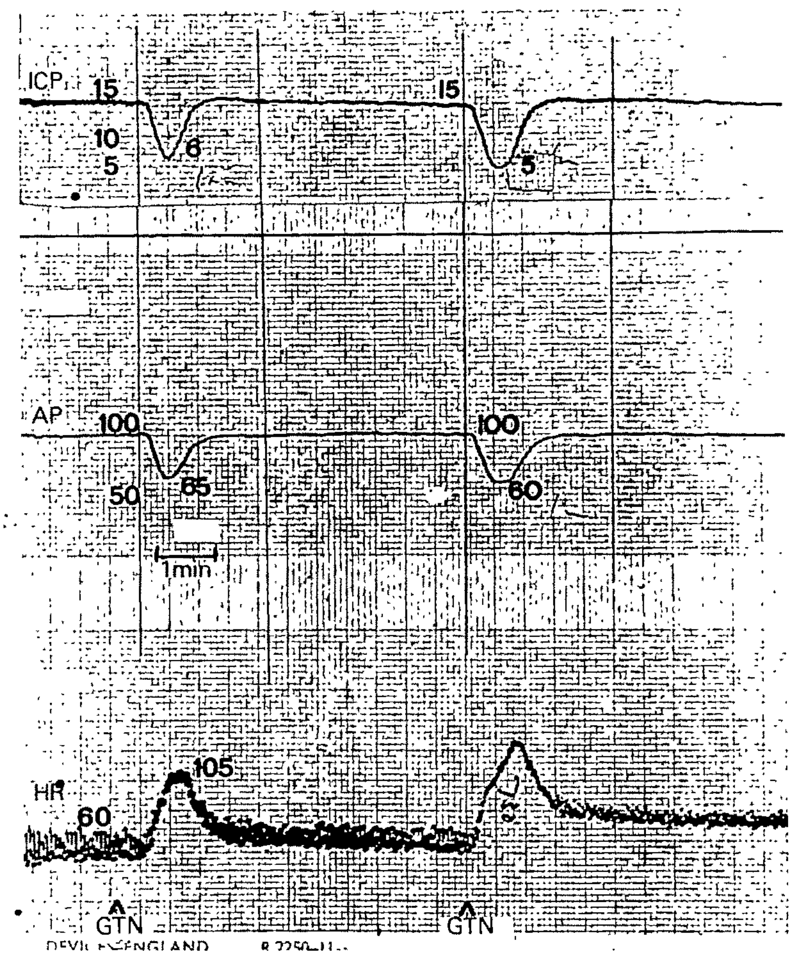

FIG. 3. Tracing showing the effect of two identical bolus doses of GTN 2.5 mg on an animal with increased i.c.p. given 5 min apart. A consistent decrease in m.a.p. and i.c.p. occurred in both instances with a return to normal values within 1.5 min.

duce appreciable hypotension (decrease in m.a.p. 34.5 ± 2.7 mm Hg) there was a consistent increase in i.c.p. (mean increase 3.1 ± 0.6 mm Hg) ($P < 0.001$) (table I). The time course of the change in i.c.p. closely followed that of the arterial pressure; maximum hypotension was achieved 30 s after injection of GTN, and a return to initial values of both m.a.p. and i.c.p. occurred within 1.5–2 min.

Once the baseline i.c.p. had been increased by inflation of the extradural balloon a different pattern of response was seen. The changes were dependent upon the extent of systemic hypotension: if the decrease in m.a.p. was less then 25% of its initial value an increase in i.c.p. similar to that seen at normal values of i.c.p. was observed.

However, when the decrease in m.a.p. was greater than 25% of its initial value there was a decrease in i.c.p. (mean 3.2 ± 0.9 mm Hg) in 19 out of 23 observations. An example is illustrated in figure 3. This decrease in i.c.p. differed significantly from the changes occurring at normal i.c.p., and those at increased i.c.p. where the decrease in arterial pressure was small.

On 11 of the 19 occasions on which there was a decrease in i.c.p., the i.c.p. increased sharply, and was observed to exceed its initial value before returning to baseline as the arterial pressure increased towards normal (fig. 4).

There was no significant difference between the baseline m.a.p. of those observations at normal

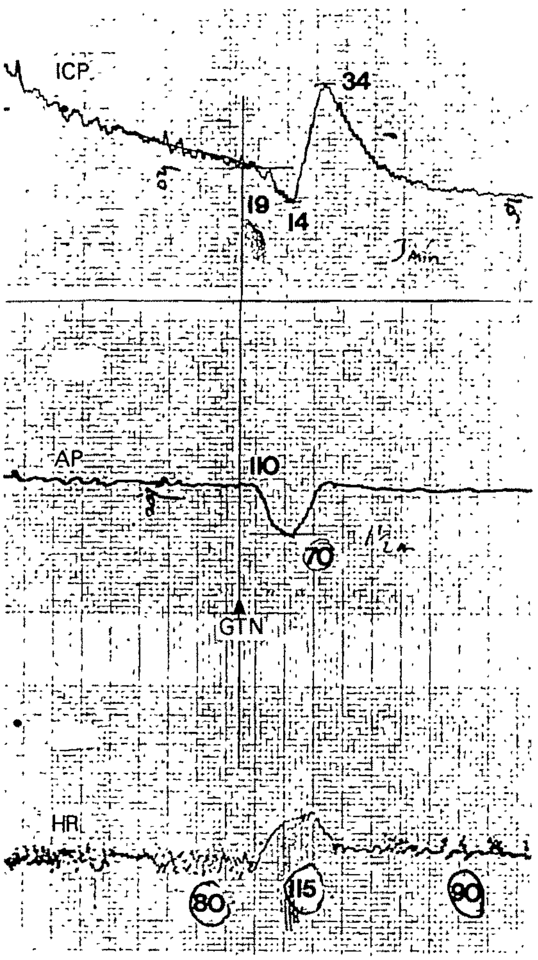

FIG. 4. Tracing at increased i.c.p. showing a rapid increase in i.c.p. occurring as m.a.p. returned to normal following a 2.5-mg bolus of GTN, which produced a 36% decrease of m.a.p. and a 5-mm Hg decrease in i.c.p.

i.c.p. and those associated with increases in i.c.p., nor any significant difference between the initial i.c.p. in the two groups with increased values of i.c.p. However, there was a significant difference between the baseline m.a.p. of those observations in which the decrease in m.a.p. was less than 25% of control, and those in which the decrease in m.a.p. was greater than 25%. This was the result of the inclusion of eight observations in the latter group in which the baseline m.a.p. was less than 100 mm Hg. These observations were included for the sake of completeness, and if analysed separately show no statistical difference in the change in i.c.p. following GTN (−2.9 ± 1.0 mm Hg) from either the 15 remaining observations (−3.1 ± 1.1 mm Hg), or the original group (table II). A similar proportion of these observations (3/6) showed an increase in i.c.p. following the initial decrease.

DISCUSSION

An attempt was made in these experiments to decrease those factors which of themselves would tend to alter intracranial pressure, whilst maintaining a technique of anaesthesia which bore some similarity to clinical practice. For that reason it was decided to avoid using nitrous oxide and the volatile anaesthetic agents, and to ventilate with an air–oxygen mixture. The mild degree of hypocapnia produced may have attenuated the responses achieved, and the actual Pa_{CO_2} at the times of injection of GTN was not measured, although end-tidal carbon dioxide analyses did not indicate that significant changes in the expired concentration of carbon dioxide had occurred between the various measurements. It was considered that fentanyl, in the doses used, would have little effect on intracranial pressure. The mixture of barbiturates was found to produce good anaesthetic conditions but the modification of the changes in intracranial pressure that is such a useful feature of barbiturates in clinical practice may have modified the response to GTN, although in most instances more than 2 h had elapsed between the induction of anaesthesia and the start of the measurements.

The mechanism of relaxation of vascular smooth muscle by which GTN exerts its hypotensive effect is incompletely understood, but is thought to involve the reduction of active nitrate to nitrite ions by tissue sulphydryl groups. Nitrite ions increase the content of intracellular cyclic AMP and stimulate a Ca^{2+} binding process in smooth muscle, thus decreasing the amount of free myoplasmic Ca^{2+} available to trigger contraction (Parratt, 1974). GTN acts predominantly on capacitance vessels (Mason and Braunwald, 1965) and results in decreases in venous return and stroke volume (Flaherty et al., 1975). It is predictable that, at normal i.c.p., the administration of GTN would produce a transient increase in i.c.p. as a result of the increase in cerebral blood volume consequent on cerebral venous dilatation. This finding has been observed in experimental animals (Chestnut et al., 1978; Rogers and Traystman, 1979a; Rogers et al., 1979; Stevenson, Traystman and Rogers, 1980). However, Rogers and Traystman (1979b) have shown that cerebral blood flow (c.b.f.) is unchanged during GTN-induced hypotension at normal values of i.c.p.

The finding that when intracranial compliance is decreased and m.a.p. decreases by more than 25% of its initial value a reversal of the change in i.c.p. is produced, is in contrast to previous work. It is suggested that under conditions of intracranial hypertension the dilatation of the thin-walled cerebral veins produced by GTN is opposed by the high i.c.p., while the arteriolar resistance is little affected. The resulting change in i.c.p. is caused by alterations in cerebral blood volume as well as changes in c.b.f. Rogers and Traystman (1979a, b) demonstrated that there was a decrease in c.b.f. during GTN hypotension when the i.c.p. was increased, even if m.a.p. was relatively high (100 mm Hg). Although, theoretically, the normal regulating mechanisms would tend to maintain near normal cerebral blood flow to an m.a.p. of 60 mm Hg, the rapid changes of arterial pressure produced by GTN may outstrip the ability of the brain to compensate. Hence, when rapid and profound decreases in arterial pressure are produced in the face of intracranial hypertension the i.c.p. will decrease. Few workers have produced decreases in m.a.p. greater than 25% of its initial value during experiments with increased i.c.p., and most have maintained cerebral perfusion pressures in excess of those obtained in our experiments. This may be in part a result of the larger doses of GTN used in our experiments: $0.05-0.2\ \mathrm{mg\,kg^{-1}}$ as opposed to $0.005-0.05\ \mathrm{mg\,kg^{-1}}$ (Rogers and Traystman, 1979a).

GTN is a drug with a short half-life of 2 min (Cottrell, Gupta and Turndorf, 1980) and produces evanescent hypotensive effects. The rapid return of arterial pressure towards baseline is responsible for the sudden increase in i.c.p. after the initial decrease. A similar effect was noted with sodium nitroprusside infusion (Turner et al., 1977) in man as a result of equally rapid changes in arterial pressure. In both cases the sudden return to normal of the arterial pressure might adversely affect intracranial dynamics in a patient with critically decreased intracranial compliance and an intact dura.

We would suggest that this, and previous studies, have demonstrated that GTN can induce systemic hypotension, and its lack of toxicity and short duration of action are advantageous. However, it can produce an increase in intracranial pressure, although the decrease in i.c.p that occurs with more marked decreases in m.a.p., in the presence of decreases in intracranial compliance may modify the decrease in perfusion pressure produced during hypotension. It would seem wise to apply the same constraints to its use in neurosurgery as has been suggested by others for sodium nitroprusside, exhibiting it only after the dura is open or following standard measures to decrease i.c.p.

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REPONSE DE LA PRESSION INTRACRANIENNE CHEZ LE CHIEN A UNE HYPOTENSION SYSTEMIQUE INDUITE PAR LA NITROGLYCERINE

RESUME

Les modifications de la pression intracrânienne (PIC), en rapport avec les chutes de pression artérielle systémique induites par la nitroglycérine ont été étudiées chez 18 lévriers. Lorsque les valeurs de la PIC sont normales (< 12 mm Hg) la nitroglycérine entraîne une augmentation de la PIC de 3,1 ± 0,6 mm Hg (moyenne ± ESM). Lorsque la PIC est augmentée (> 12 mm Hg), une faible diminution de la pression artérielle moyenne (PAM) (< 25% de la valeur contrôle) s'accompagne d'une augmentation de 4,7 ± 0,5 mm Hg, tandis qu'une diminution plus marquée de la PAM (> 25% de la valeur contrôle) s'accompagne d'une diminution de 3,2 ± 0,9 mm Hg de la PIC. Dans 11 observations sur 19 où une diminution de la PIC est apparue en association avec des hypotensions systémiques, il y a eu une augmentation rebond de la PIC lorsque la PAM a été ramenée aux valeurs contrôles.

Nous suggérons que la PIC soit abaissée avant que cet agent soit utilisé pour induire une hypotension en neurochirurgie.

DAS VERHALTEN DES INTRAKRANIELLEN DRUCKES AUF DURCH NITROGLYZERIN AN KANINCHEN HERVORGERUFENE HYPOTENSION

ZUSAMMENFASSUNG

Veränderungen des intrakraniellen Druckes (IKD) in Beziehung zum Absinken des systemischen arteriellen Druckes wurden an 18 Windhunden untersucht. Bei normalem IKD (12 mm Hg) rief die Blutdruckabnahme einen Anstieg des IKD von 3,1 ± 0,6 mm Hg (Mittelwert ± Standardabweichung) hervor. Bei erhohtem IKD (12 mm Hg) ging geringes Absinken des mittleren arteriellen Druckes (MAD) (25% der Kontrollwerte) mit einem Anstieg von 4,7 mm Hg ± 0,5 einher, wohingegen stärkeres Absinken des MAD (grösser als 25% der Kontrollwerte) ein Absinken des IKD von 3,2 ± 0,9 mm Hg nach sich zog. Elf von 19 der beobachteten Fälle, bei denen ein Absinken des IKD in Verbindung mit dem systemischen Blutdruckabfall stattfand, stellte sich ein rebound-Anstieg des MAD ein. Es empfahlt sich, den IKD herabzusetzen, bevor dieses Mittel zur Blutdruckssenkung bei neurochirurgischen Eingriffen eingesetzt wird.

LA RESPUESTA DE LA PRESION INTRACRANEAL CANINA A LA HIPOTENSION SISTEMICA INDUCIDA POR NITROGLICERINA

SUMARIO

En 18 perros galgos, se estudiaron los cambios de presión intracraneal en relación con las disminuciones de la presión arterial sistémica producidas por nitroglicerina. A los valores normales del i.c.p. (< 12 mmHg), el GTN produjo un aumento del i.c.p. de 3,1 (± 0,6) mmHg (promedio ± SEM). En condiciones de aumento del i.c.p. (12 + mmHg), se manifestaron pequeñas disminuciones de la presión arterial media (m.a.p.) (<25% del control) asociadas con un aumento de 4,7 (±0,5) mmHg, mientras que mayores disminuciones del m.a.p. (>25% del control) fueron asociadas con una disminución de 3,2 (±0,9) mmHg del i.c.p. En 11 de las 19 observaciones en que ocurrió una disminución de la presión intracraneal en asociación con la hipotensión sistémica, hubo un aumento de rebote del i.c.p. cuando se restableció el m.a.p. Se sugiere que se haga bajar el i.c.p. antes de usar esta substancia para producir la hipotensión durante la neurocirujía.

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CARDIORESPIRATORY RESPONSES TO AN I.V. INFUSION OF DOBUTAMINE IN THE INTACT ANAESTHETIZED DOG

C. H. ORCHARD, M. K. CHAKRABARTI AND M. K. SYKES

SUMMARY

The cardiorespiratory responses to an i.v. infusion of dobutamine hydrochloride were assessed in eight anaesthetized, mechanically ventilated dogs. As the rate of infusion of dobutamine was increased from 2 to 30 $\mu g\,kg^{-1}\,min^{-1}$, there was a progressive decrease in arterial pressure, pulmonary wedge pressure and arterial pH. There was a significant decrease in arterial oxygen tension at the greater doses of dobutamine (15 and 30 $\mu g\,kg^{-1}\,min^{-1}$) from initial control values. Carbon dioxide output, arterial carbon dioxide tension, venous admixture and oxygen consumption increased during the infusion of dobutamine. However, oxygen supply increased further so that the oxygen consumption: supply ratio decreased. It is concluded that dobutamine may decrease arterial oxygen tension, but that the increased cardiac output and decreased arterial pH produced by dobutamine may increase oxygen supply to the tissues in spite of this.

Dobutamine hydrochloride (Dobutrex) is a new β_1 adrenergic agonist, developed by systematic modification of isoprenaline (Tuttle and Mills, 1975). The most common clinical inotropic agents, isoprenaline and dopamine, have actions apart from those on the heart and have both been shown to cause arterial hypoxaemia (Fordham and Resnekov, 1968; Lemaire et al., 1976). It was of interest, therefore, to look at the cardiorespiratory effects of the new, relatively cardiospecific synthetic catecholamine, dobutamine hydrochloride, given in a series of doses within the range used clinically (2–30 $\mu g\,kg^{-1}\,min^{-1}$) to anaesthetized, mechanically ventilated dogs.

METHODS

Eight dogs of various breeds, weights 20–36 kg (mean ± SEM = 22.7 ± 2.54 kg) were anaesthetized with thiopentone 20–30 $mg\,kg^{-1}$ and pentobarbitone 60–240 mg. The dogs were placed supine in a V-shaped trough, intubated, and ventilated at 15 b.p.m. via a non-rebreathing valve (Sykes, 1969) from which expired gas could be collected. Tidal volume was adjusted to give an end-tidal carbon dioxide concentration close to 4.5%. The right femoral artery and vein were cannulated for measurement of cardiac output by dye dilution. The left femoral artery was cannulated for mean aortic pressure ($\overline{PAO}$) measurement and the withdrawal of arterial blood samples. The left femoral vein was cannulated for the administration of dobutamine and saline. A cannula was passed through the right external jugular vein into the pulmonary artery for the measurement of mean pulmonary artery pressure ($\overline{PPA}$) and the withdrawal of mixed venous blood samples. Mean pulmonary wedge pressure ($\overline{Pw}$) was measured via a pulmonary artery catheter passed from the left external jugular vein. All pressures were measured using Consolidated Electrodynamics strain gauges and a heated stylus recorder. Anaesthesia was maintained with increments of thiopentone and pentobarbitone administered via a cannula placed in the left cephalic vein. Dog temperature, measured using a thermistor placed in the lower half of the oesophagus, was maintained at a mean temperature of 36.8 °C ± 0.2 (± SEM) by means of a heater under the trough.

The experimental programme consisted of an initial control period during which saline was infused into the left femoral vein at 0.1 $ml\,min^{-1}$ by a calibrated infusion pump. The infusion was then changed to dobutamine infused at the same rate to give a dose of 2 $\mu g\,kg^{-1}\,min^{-1}$. The infusion rate was subsequently increased to give doses of 7.5, 15 and 30 $\mu g\,kg^{-1}\,min^{-1}$ of dobutamine followed by a final control period in which saline was infused at the same rate as the final dose of dobutamine

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(1.5 ml min^{-1}). Each period of drug infusion lasted approximately 20 min. The time between the cessation of the dobutamine infusion and the final control measurements was at least 45 min. The total volume of fluid infused was never greater than 150 ml, and the time taken to complete the programme never exceeded 3.5 h.

When a steady state had been reached, determined by vascular pressures and end-tidal carbon dioxide, a full set of measurements was taken in each control period and during each rate of dobutamine infusion. This consisted of drawing arterial and mixed venous blood samples which were analysed in duplicate for $P\text{O}_2$, $P\text{CO}_2$, pH and haemoglobin concentration, duplicate measurements of cardiac output, measurement of $\overline{P\text{AO}}$, $\overline{P\text{PA}}$, $\overline{P\text{W}}$, end-tidal carbon dioxide, mixed expired carbon dioxide and oxygen concentrations, expired gas temperature and volume and airway pressure (measured between the endotracheal tube and the collect valve).

Alveolar–arterial $P\text{O}_2$ difference ($P\text{AO}_2 - P\text{aO}_2$), venous admixture ($\dot{Q}\text{va}/\dot{Q}\text{t}$), oxygen uptake ($\dot{V}\text{O}_2$), carbon dioxide production ($\dot{V}\text{CO}_2$) and physiological deadspace ($V\text{D}/V\text{T}^{\text{phys}}$) were calculated from the measured variables using the computer program of Adams (1970) which uses standard formulae. Pulmonary vascular resistance (PVR), oxygen supply ($\dot{Q} \times \text{CaO}_2$) and oxygen consumption : supply were also calculated.

Statistical analysis of normally distributed variables was by a two-way analysis of variance followed by Duncan's multiple range test between treatments where indicated as necessary by the analysis of variance. Non-parametric variables ($\dot{Q}\text{va}/\dot{Q}\text{t}$ and $V\text{D}/V\text{T}^{\text{phys}}$) were analysed using a two-way non-parametric analysis of variance followed by a paired Wilcoxon's test.

RESULTS

The responses to the different doses of dobutamine are shown below:

2 μg kg^{-1} min^{-1}. At this infusion rate there were no significant changes in any of the measurements.

7.5 μg kg^{-1} min^{-1}. There was a significant ($P < 0.05$) decrease in pulmonary wedge pressure compared with the initial control value. No other measurements showed a significant change.

15 μg kg^{-1} min^{-1}. This dose rate produced a further decrease in wedge pressure and also a significant decrease in arterial oxygen tension from control values ($P < 0.05$). There was an increase in oxygen consumption ($P < 0.01$) and in arterial and end-tidal carbon dioxide tensions from control values ($P < 0.05$ and $P < 0.01$ respectively).

30 μg kg^{-1} min^{-1}. In addition to the changes which occurred with an infusion rate of 15 μg kg^{-1} min^{-1}, there was also a significant decrease from control values of arterial pH ($P < 0.01$), arterial pressure ($P < 0.01$) and an increase in carbon dioxide output ($P < 0.01$) and venous admixture ($P < 0.01$) from control values.

Although oxygen consumption increased significantly during infusion of dobutamine, oxygen supply increased further, so that the oxygen consumption : supply ratio decreased during the dobutamine infusion. However, this was greater than the initial control values during the final control period.

No significant changes in airway pressure, $\overline{P\text{PA}}$, PVR, ($P\text{AO}_2 - P\text{aO}_2$) and $\dot{Q}\text{t}$ occurred.

The cardiovascular measurements are summarized in table I and respiratory measurements in table II. Changes in blood-gases, vascular pressures and cardiac output and oxygen consumption and supply are shown in figures 1, 2, and 3.

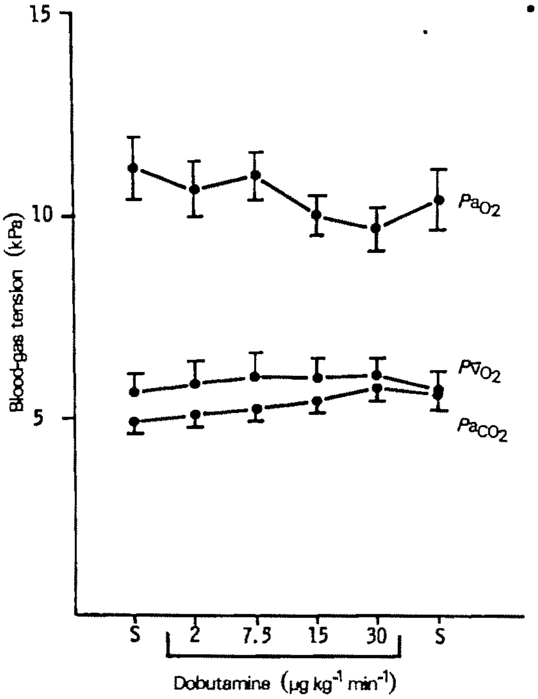

FIG. 1. Changes in mean (± SEM) blood-gas tensions during the infusion of dobutamine. S = saline infusion during control period.

TABLE I. *The effect of dobutamine on the cardiovascular system (mean ± SEM). Arabic numerals below means ± SEM denote significance:* $^{*}P < 0.05$; $^{**}P < 0.01$

		Dobutamine infusion				
	1 Saline	2 (2 μg kg^{-1} min^{-1})	3 (7.5 μg kg^{-1} min^{-1})	4 (15 μg kg^{-1} min^{-1})	5 (30 μg kg^{-1} min^{-1})	6 Saline
$\overline{P}_{AO}$ (mm Hg)	139.2 ±11.8 5**, 6*	128.8 ±11.2 5*	130.3 ±7.8 5*	123.3 ±8.1	105.8 ±12.9	114.2 ±8.6
$\overline{P}_{PA}$ (mm Hg)	13.3 ±1.3	12.5 ±1.6	12.7 ±1.8	12.2 ±1.8	12.3 ±2.0	11.8 ±1.3
$\overline{P}_{W}$ (mm Hg)	3.3 ±0.8 3*, 4** 5**	2.3 ±0.8	1.7 ±0.9	1.2 ±0.7 6*	1.2 ±0.8 6*	2.7 ±0.7
$\dot{Q}$ (litre min^{-1})	1.81 ±0.65	1.93 ±0.66	2.56 ±0.68	2.43 ±0.57	2.63 ±0.63	1.62 ±0.50
PVR (mm Hg litre^{-1} min^{-1})	5.53 ±3.23	5.29 ±3.00	4.30 ±2.70	4.53 ±3.60	4.22 ±2.40	5.62 ±3.38

DISCUSSION

In this study, some measurements during the final control period were significantly different from those made during the initial control period. All measurements were, however, returning towards the initial control values. This suggests either a time effect, or that dobutamine, despite a plasma half-life of only 2 min in the dog (Fasola, Lemberger and Murphy, 1976; Murphy, Williams and Kau, 1976) has an action, or products of its action, which persist for longer than 45 min (the time between S_5 and S_6). However, the recorded values were stable before the final control measurements were taken, which suggests a time effect caused by a change in condition of the preparation. The short half-life of dobutamine and the stability of measurements when a sample was taken at a particular infusion rate suggest that, despite a cumulative infusion, the effect seen at each dose rate represented those produced by that infusion rate. This view is partly supported by the findings of Anggård and colleagues (1978) who showed that, 30 min after discontinuing a dobutamine infusion, the plasma concentration of the drug had returned to the control value.

Although the plasma dobutamine concentration was not measured in the present study, Anggård and others showed a linear correlation between the infusion rate of dobutamine and plasma concentrations, with an infusion rate of 5 μg kg^{-1} min^{-1} giving a mean plasma concentration of 65 ng ml^{-1} and an infusion rate of 15 μg kg^{-1} min^{-1} giving a mean plasma concentration of 190 ng ml^{-1}. There were, however, large variations between individuals.

Oxygen consumption and carbon dioxide production

The cumulative infusion of dobutamine in the present study was associated with an increase in oxygen consumption and carbon dioxide production. The stimulatory effects of β-agonists on metabolism have long been recognized (Himms Haagen, 1967) and are observed during the administration of isoprenaline i.v. to dogs (Finlay, Wightman and Sykes, 1970), of dopamine i.v. to dogs (Hall, Young and Scott, 1979) and of salbutamol, a β_2-agonist, to asthmatic patients either orally or i.v. (Neville et al., 1977). However, in the present study oxygen supply also increased and the oxygen consumption : supply ratio decreased.

Arterial oxygen tension

The significant decrease in arterial oxygen tension observed in this study during the infusion of dobutamine at 15 and 30 μg kg^{-1} min^{-1} has also been shown during the infusion of dopamine to patients (Lemaire et al., 1976) and during the infusion of isoprenaline to dogs (Finlay, Wightman and Sykes, 1970) and to patients (Knudson and Constantine,

TABLE II. *The effect of dobutamine on the respiratory system (mean ± SEM or mean and range). Arabic numerals below means ± SEM denote significance:* $^*P < 0.05$; $^{**}P < 0.01$

		Dobutamine infusion				
	1 Saline	2 (2 μg kg^{-1} min^{-1})	3 (7.5 μg kg^{-1} min^{-1})	4 (15 μg kg^{-1} min^{-1})	5 (30 μg kg^{-1} min^{-1})	6 Saline
Pa_{O_2} (kPa)	11.22 ±0.67 4*, 5**	10.70 ±0.68	11.08 ±0.61 4*, 5**	9.98 ±0.45	9.75 ±0.46	10.42 ±0.59
Pa_{CO_2} (kPa)	4.85 ±0.19 4*, 5**, 6**	5.05 ±0.23 5**	5.20 ±0.16 5*	5.39 ±0.28	5.76 ±0.28	5.57 ±0.34
Arterial pH (unit)	7.319 ±0.013 5**, 6**	7.306 ±0.012 5**, 6**	7.300 ±0.011 5**, 6**	7.277 ±0.019 5*, 6*	7.226 ±0.022	7.238 ±0.03
$P\bar{v}_{O_2}$ (kPa)	5.62 ±0.40	5.83 ±0.43	6.03 ±0.39	5.96 ±0.40	5.97 ±0.31	5.53 ±0.34
$(PA_{O_2} - Pa_{O_2})$ (kPa)	3.22 ±0.67	3.31 ±0.65	2.83 ±0.83	3.38 ±0.44	3.51 ±0.50	3.19 ±0.59
$\dot{Q}va/\dot{Q}t$ (%)	11.4 0.5–21.1 5**	14.4 1.7–28.0 5*	15.1 1.4–32.5 5*	18.9 7.8–32.2	24.0 8.8–44.4	17.0 2.0–47.5
V_D/V_T (%)	40.4 29.2–55.7 5**	42.1 32.6–57.5	42.2 30.6–57.1	41.4 24.8–56.5	42.2 30.5–54.0	43.0 33.9–57.2
O_2 consumption (mmol min^{-1})	4.80 ±0.52 4**, 5*	4.84 ±0.60 4*	5.02 ±0.64 4*	5.60 ±0.66	5.47 ±0.49	5.15 ±0.73
CO_2 output (mmol min^{-1})	4.14 ±0.46 5**	4.03 ±0.44 5**, 6*	4.17 ±0.40 5*	4.30 ±0.40	4.61 ±0.43	4.39 ±0.50
O_2 supply (mmol min^{-1})	15.64	16.01	21.02	21.04	21.67	12.7
$\frac{O_2 \text{ consumption}}{O_2 \text{ supply}}$	0.31	0.29	0.24	0.27	0.25	0.40

1967; Fordham and Resnekov, 1968; Palmer and Diament, 1968; Palmer et al., 1970). However, unlike that of dopamine, the action of dobutamine does not appear to depend on the release of endogenous catecholamines (Bodem, Skelton and Sonnenblick, 1974) nor, as in the case of dopamine, is it likely to be further converted to another active form.

The decrease in arterial oxygen tension in this study was accompanied by a decrease in pH, principally caused by an increase in carbon dioxide tension, although at 30 μg kg^{-1} min^{-1} there was also a metabolic component to the acidosis. This may, in part, have been caused by the low pH of the infused dobutamine (pH = 6.1). This decreased pH would cause the oxygen dissociation curve to shift to the right so that, without changing diffusion gradients into the tissue, oxygen supply to the tissue would increase. The decrease in the oxygen consumption : supply ratio would tend to increase $P\bar{v}_{O_2}$ and, in the presence of a constant right to left shunt fraction, would tend to increase Pa_{O_2}. However, changes in $P\bar{v}_{O_2}$ were not significant in this study.

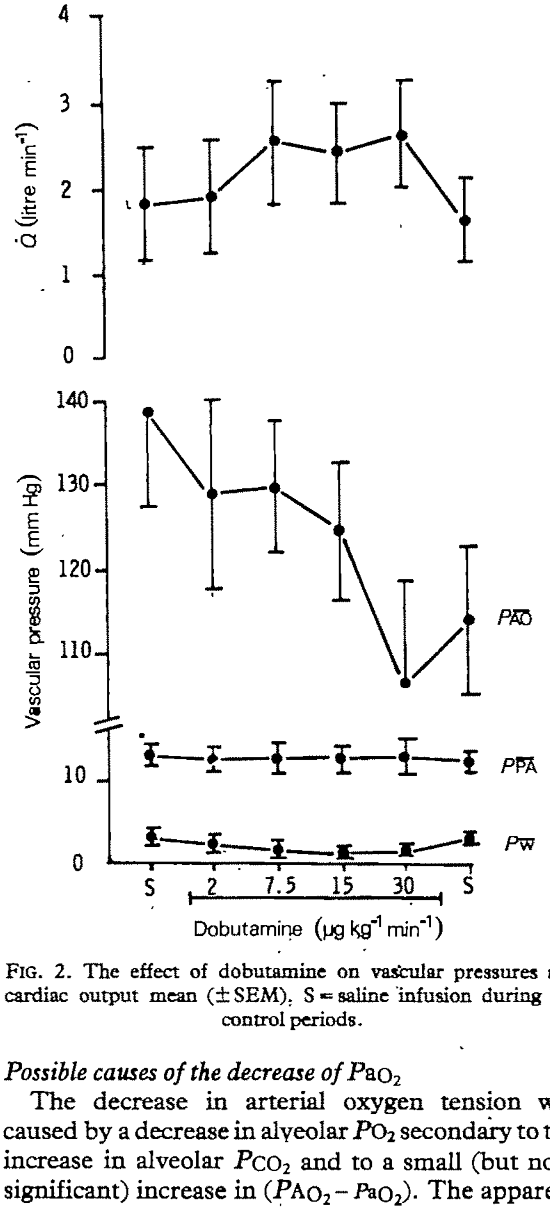

FIG. 2. The effect of dobutamine on vascular pressures and cardiac output mean (±SEM). S = saline infusion during the control periods.

Possible causes of the decrease of Pa_{O_2}

The decrease in arterial oxygen tension was caused by a decrease in alveolar P_{O_2} secondary to the increase in alveolar P_{CO_2} and to a small (but non-significant) increase in ($PA_{O_2} - Pa_{O_2}$). The apparent discrepancy between the significant increase in venous admixture and the non-significant change in ($PA_{O_2} - Pa_{O_2}$) may be caused by the increase in mixed venous P_{O_2} resulting from the reduction in oxygen consumption : supply ratio, the hypoxaemia resulting from the increase in venous admixture being offset by the greater P_{O_2} of the blood coming from the areas of lung with a low ventilation : perfusion ratio.

The cause of the increased venous admixture is uncertain although it has been noted previously (Gauthier-Lafaye, 1978). There were no significant changes in $P\overline{PA}$ nor in V_D/V_T ratios and therefore no major changes in the distribution of blood flow between the upper and lower parts of the lung. PVR decreased, but not significantly, and this effect may have been caused by increase in cardiac output. Two possible causes of the decreased Pa_{O_2} therefore remain: first, that shunt channels may have been opened by the increase in cardiac output, although the changes in cardiac output did not attain significance. Second, the $P\bar{v}_{O_2}$ of the blood from post-pulmonary shunt sources may have decreased. Although a decreased $P\overline{AO}$ does not alter anatomical shunt (Aviado et al., 1961) it may decrease bronchial flow, which may reduce bronchial venous P_{O_2}. Increased oxygen extraction by the myocardium would also result in a decrease in the P_{O_2} of Thebesian vein blood.

Increased carbon dioxide tensions have been shown to increase venous admixture, but only by a non-significant amount and at carbon dioxide tensions far greater than those achieved in the present study (Finlay, Wightman and Sykes, 1970). The results of this study do not, therefore, help elucidate the cause of the increased venous admixture observed.

Cardiovascular measurements

The magnitude of the changes in cardiac output observed are comparable to those of Vatner, McRitchie and Braunwald (1974) who showed a 43% increase in cardiac output of conscious dogs with an infusion of 20 µg kg⁻¹ min⁻¹ of dobutamine and an 80% increase of cardiac output with an infusion rate of 40 µg kg⁻¹ min⁻¹. However, these workers found a minimal increase in arterial pressure, whereas the present study showed a significant decrease of arterial pressure during the infusion of 30 µg kg⁻¹ min⁻¹ of dobutamine. The present decrease in $P\overline{AO}$ may be a result of either the systemic dilator action of a decreased pH or the β-agonist effects of dobutamine on the systemic vasculature (Vatner, McRitchie and Braunwald, 1974). Tinker and others (1976) also found that dobutamine 5 µg kg⁻¹ min⁻¹ and 10 µg kg⁻¹ min⁻¹ given i.v. to cardiac patients recovering from surgery increased mean arterial pressure by 12%. However, dobutamine also increased cardiac output significantly.

The inotropic effects of dobutamine have been well documented (Glynne and Lucas, 1978), as have its peripheral adrenergic agonist effects (Robie,

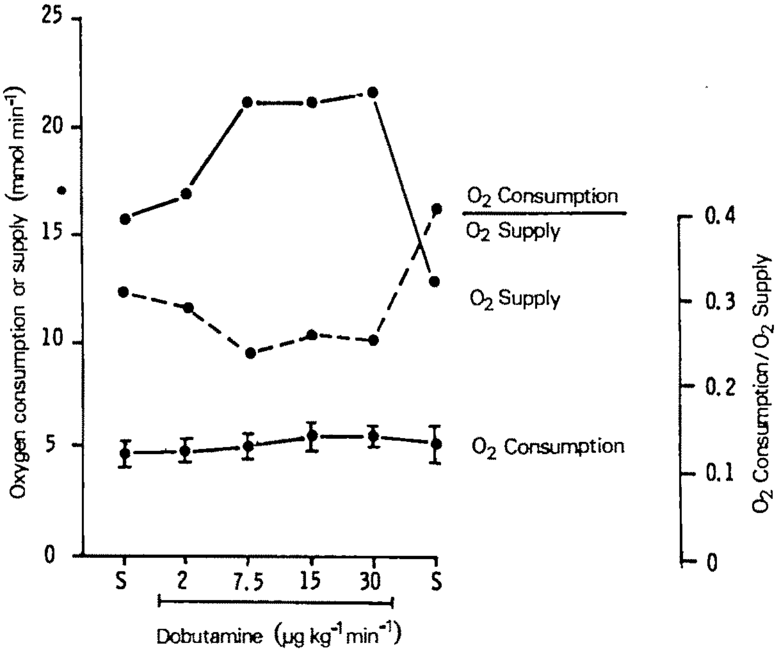

FIG. 3. Oxygen consumption (mean ± SEM), oxygen supply and oxygen consumption: supply ratio during the infusion of dobutamine. S = saline infusion during control periods.

Nutter and McNay, 1973; Robie et al., 1974; Vatner, McRitchie and Braunwald, 1974). From the present study, it appears that the overall cardiorespiratory effect will be a balance of several different factors and may vary between individuals depending on their initial condition.

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REPONSES CARDIORESPIRATOIRES A UNE PERFUSION INTRAVEINEUSE DE DOBUTAMINE CHEZ LE CHIEN INTACT ANESTHESIE

RESUME

Les réponses cardiovasculaires à une perfusion intraveineuse de chlorhydrate de dobutamine ont été étudiées chez huit chiens anesthésiés en ventilation contrôlée. Lorsqu'on augmente le débit de perfusion de 2 à 30 μg kg^{-1} min^{-1}, il y a une diminution progressive de la pression artérielle, de la pression capillaire pulmonaire et du pH artériel. Il y a une diminution significative de la pression partielle artérielle d'oxygène aux posologies les plus élevées de dobutamine (15 et 30 μg kg^{-1} min^{-1}) par rapport aux valeurs initiales contrôles. Le débit de dioxyde de carbone, la pression partielle artérielle du dioxyde de carbone, la différence artério-veineuse et la consommation d'oxygène augmentent pendant la perfusion de dobutamine. Cependant, la fourniture d'oxygène augmente encore plus de telle sorte que le rapport oxygène consommé : oxygène fourni diminue. Nous en concluons que la dobutamine peut diminuer la pression partielle artérielle en oxygène mais que l'augmentation du débit cardiaque et la diminution du pH artériel induites par la dobutamine peut augmenter malgré ce fait la quantité d'oxygène délivrée aux tissus.

AUSWIRKUNGEN EINER INFUSION VON DOBUTAMIN AUF DIE HERZ- UND ATEMFUNKTION BEIM GESUNDEN NARKOTISIERTEN HUND

ZUSAMMENFASSUNG

Die Auswirkungen einer i.v. Infusion von Dobutamin auf die Herz- und Atemfunktion wurden bei fünf narkotisierten und künstlich beatmeten Hunden gemessen. Eine Erhöhung der Infusionsmenge von Dobutamin von 2 auf 30 μg kg^{-1} führte zu fortschreitendem Abfall des arteriellen Druckes des pulmonary wedge Druckes und des arteriellen pH. Der arterielle Sauerstoffdruck nahm mit dem höheren Dobutamin Dosien (15 und 30 μg kg^{-1} min^{-1}) signifikant gegenüber anfänglichen Kontrollwerten ab. Die CO_2-Abgabe, der arterielle CO_2-Druck, die venöse Blutbeimischung und der Sauerstoffverbrauch nahmen während der Infusion von Dobutamin zu. Die Sauerstoffzufuhr stieg jedoch weiter an, so dass Verhältnis Sauerstoffverbrauch/Sauerstoffzufuhr abnahm. Wir schliessen daraus, dass Dobutamin den arteriellen Sauerstoffdruck erniedrigen kann dass aber das durch Dobutamin bedingte erhöhte Herzminutenvolumen und der erniedrigte arterielle pH trotzdem zu einer erhöhten Sauerstoffversorgung der Gewebe führen kann.

RESPUESTAS CARDIORESPIRATORIAS A UNA INFUSION I.V. DE DOBUTAMINA EN EL PERRO ANESTESIADO INTACTO

SUMARIO

Se evaluó las respuestas cardiorespiratorias a una infusión i.v. de hipocloruro de dobutamina en ocho perros anestesiados mecánicamente ventilados. A medida que aumentaba el ritmo de infusión de dobutamina de 2 a 30 μg kg^{-1} min^{-1}, tuvo lugar una disminución progresiva de la presión arterial, de la presión respiratoria de calce y del pH arterial. Hubo una reducción significativa de la tensión de oxígeno arterial en las dosis mayores de dobutamina (15 y 30 μg kg^{-1} min^{-1}) en relación con los valores de control iniciales. La producción de anhídrido carbónico, la tensión arterial de anhídrido carbónico, la mezcla venosa y el consumo de oxígeno aumentaron durante la infusión de dobutamina. Sin embargo, el suministro de oxígeno aumentó aún más de manera que la relación consumo de oxígeno/suministro de oxígeno descendió. Se concluye que la dobutamina puede hacer bajar la tensión arterial del oxígeno, pero que el ritmo cárdiaco en aumento y el pH arterial en disminución producidos por la dobutamina pueden hacer aumentar el suministro de oxígeno a los tejidos a pesar de ello.

Br. J. Anaesth. (1982), 54, 681

A SANDWICH ELECTRODE FOR MULTI-GAS ANALYSIS: A PROTOTYPE

C. E. W. HAHN, E. A. H. HALL, P. MAYNARD AND W. J. ALBERY

SUMMARY

A prototype composite electrode consisting of a metallized membrane "outer" cathode, and a conventional "inner" silver disc cathode, both sharing the same electrolyte, is described. Preliminary results indicate that the metallized membrane will act as an oxygen filter, allowing anaesthetic gases such as nitrous oxide, to pass through to the second (inner) cathode, where they may be reduced. Linear relationships exist for oxygen concentration and metallized membrane current; and for nitrous oxide concentration and the second cathodic current. Extension of this technique to measure both halothane and nitrous oxide on the second cathode, simultaneously with oxygen on the metallized membrane, is discussed.

Recent studies (Albery et al., 1978; Brooks et al., 1978, 1980; Hahn et al., 1979) have shown that both oxygen and nitrous oxide can be measured simultaneously on a single electrode using pulse polarography. The application of these techniques (together with conventional polarography) to blood-gas analysis has been reviewed by Hahn (1980, 1981).

A more recent paper by the same authors (Albery, Hahn and Brooks, 1981) has described the polarographic measurement on silver cathode surfaces and concluded that halothane could be quantitatively reduced on silver, but only in the absence of oxygen. This is because oxygen and halothane are reduced at the same potential on silver surfaces and can therefore not be discriminated unless one is removed. Halothane can be removed by using an impermeable membrane, such as Teflon, but this defeats the purpose of the exercise of simultaneous measurement.

We have therefore focused our attention on a means of removing oxygen from the primary measuring system, but at the same time being able to measure its concentration quantitatively. This paper describes an electrochemical oxygen filter combined in a composite electrode system, which we will call a "sandwich" electrode. The oxygen filter is a metallized membrane, based on the designs of Bergman (1966, 1968, 1974), Bergman and Windle (1972) and Bartlett, Dobson and Eastham (1980). The rest of the electrode is a conventional polarographic cell, which shares the same electrolyte as the metallized membrane oxygen filter. A prototype electrode is described, together with preliminary experiments confirming its application as a multigas sensor.

METHODS

Sandwich electrode design

The design of the prototype sandwich electrode is outlined in figure 1. The body was turned out of a cylindrical block of Teflon, with the inner cavity filled with the electrolyte solution. A series of conducting holes ensured contact between electrolyte reservoir and the electrode elements. These con-

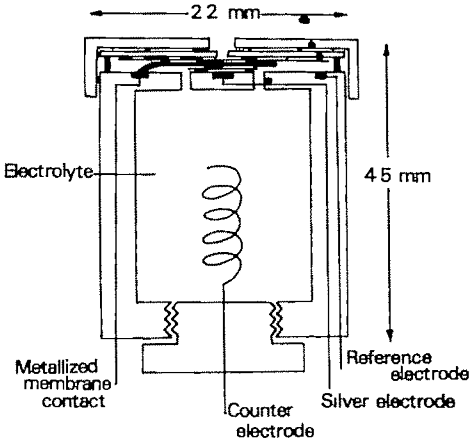

FIG. 1. Schematic cross-sectional view of the composite sandwich electrode. A nylon spacer is inserted between the metallized membrane and the inner (second) cathode.

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sisted of a conventional silver disc cathode (3 mm diameter) set flush into the upper surface of the Teflon cylinder, together with a miniature silver/silver chloride reference electrode and a silver stud for making contact with the metallized membrane.

The metallized membrane consisted of a conventional silicone or Teflon membrane with one surface coated with a thin layer of gold or silver on gold, which had been deposited by vacuum evaporation. Our prototype membranes were either coated for us by Dr J. V. Dobson of Newcastle University, or were kindly supplied by Dr K. Gibbs of Southampton University. The details for coating the membranes have been elucidated by Bergman (1966), and typical metal layers of 5–10 nm are recommended by him. This metal layer provides a uniform and sufficient area for the electrode processes to be diffusion controlled, even if the metal film is transparent (Bergman, 1966). Electrical contact is made with the metallized film through a coating of epoxy silver Araldite on the silver stud, as shown in figure 1.

A silver wire counter electrode was inserted into the internal electrolyte reservoir. The membrane was held in position by a Teflon cap, which was screwed "finger tight" onto the outer body of the composite electrode. The metal film was electrically separated from the second silver cathode by a thin nylon spacer, which also helped to spread a uniform electrolyte layer under the metal film.

The electrical circuitry was analogous to that previously described by us for use with a rotating ring-disc electrode (Hahn, Davis and Albery, 1975), such that both cathodes shared the same counter and reference electrode. In this instance, however, the metal film replaced the ring electrode. The polarizing potentials for both the metallized membrane and the second cathode were obtained from standard voltage sources.

Full details of the electrode design are contained in a European patent application (0027005).

Electrode pilot studies

All pilot studies for the prototype electrode were conducted at room temperature. The electrolyte solution was potassium hydroxide 0.05 mol litre^{-1}, potassium chloride 0.1 mol litre^{-1}, although any conventional $P\text{O}_2$ electrolyte solution could have been used. White spot nitrogen, room air and pure oxygen gases were used to test the membrane metal film electrode characteristics, and oxygen in nitrous oxide gas mixtures, obtained from a Wosthoff gas mixing pump (M500/a) tested the response of the second cathode.

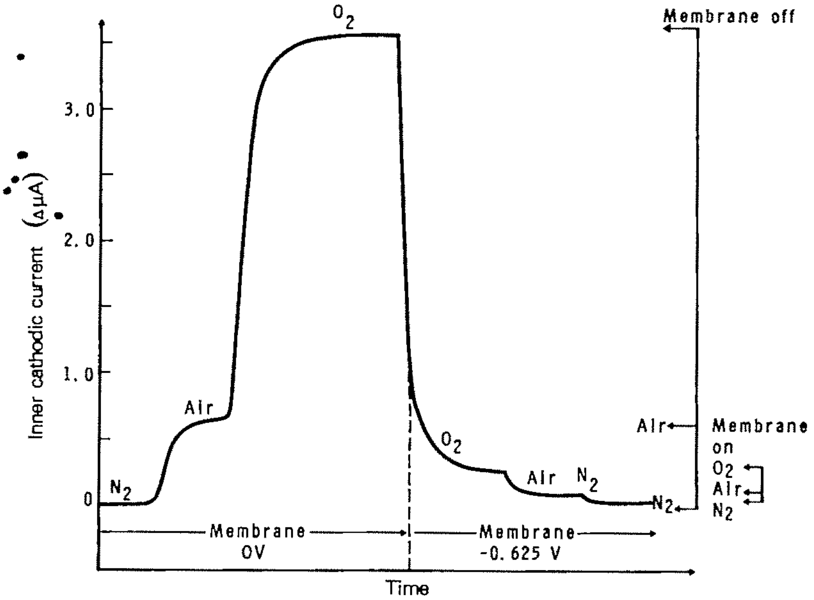

FIG. 2. The current response of the inner (second) cathode, when polarized at − 0.72 V, to nitrogen, air and pure oxygen. Left: response with metallized membrane at 0 V. Right: response with metallized membrane acting as an oxygen filter at − 0.625 V.

Oxygen filter

The oxygen filtering capacity of the metallized membrane polarized at − 0.625 V (*v.* Ag/AgCl) was investigated, using the second cathode as an oxygen detector to determine if any oxygen managed to pass through both the plastic membrane and the metal film. This was achieved by observing the nitrogen zero current, and the pure oxygen current, on the second cathode with the metallized membrane polarized first at 0 V and then − 0.625 V. The difference between the observed currents gave an indication of the oxygen-filtering capability of the metallized film.

Nitrous oxide response of second cathode

The nitrous oxide response of the second cathode was tested with the metallized film polarized continuously at − 0.65 V. Preliminary studies were conducted with the silver cathode polarized at − 0.65 V and then at − 0.72 V. Gas mixtures of 10, 15, 25, 50 and 75% (v/v) nitrous oxide in oxygen were introduced to the electrode and the response of the second cathode to the mixtures was recorded on a Bryans 29000 A3 *X/Y/t* recorder used in the *Y/t* mode.

Subsequent studies were conducted with the second cathode pulsed (using a hand-operated switch) at polarizing voltages at − 0.72 V for 170 s, with a pause of 100 s between pulses. The silver metallized membrane was continuously polarized at − 0.52 V and nitrous oxide in oxygen gas mixtures of 0, 25, 50, 75 and 100% (v/v) nitrous oxide in oxygen were used. The current transients from the pulsed cathode were recorded and the height of the current response at the end of the voltage pulse was read off.

RESULTS AND DISCUSSION

Oxygen filter membrane studies

The results of the initial oxygen studies are shown in figures 2 and 3. Figure 2 shows the current response for the silver cathode (continuously polarized at − 0.72 V) with the membrane switched off (0.0 V) and then switched on at − 0.625 V. Both the air and oxygen signals decreased to approximately 10% of their former value, as soon as the membrane was polarized, demonstrating a clear filtering effect at the metallized membrane surface. Figure 3 shows the corresponding metallized membrane current when the polarizing potential was applied in the presence of nitrogen, air and pure oxygen. A linear response is clearly demonstrated between electrode current and oxygen concentration, even though the membrane was polarized in the pulse mode.

Bergman (1974) has demonstrated that the metallized membrane gives a linear response to oxygen concentration when polarized continuously, but we believe that these initial results indicate that such a membrane can be pulsed and that it can act as an effective oxygen filter even when pulsed. In practice the membrane would be polarized at a voltage high enough to reduce oxygen but low enough not to reduce nitrous oxide (Brooks, 1980). This would ensure the passage of nitrous oxide through the membrane to the second cathode.

Nitrous oxide reduction

Figure 4 shows the response of the second silver cathode to changing concentrations of nitrous oxide

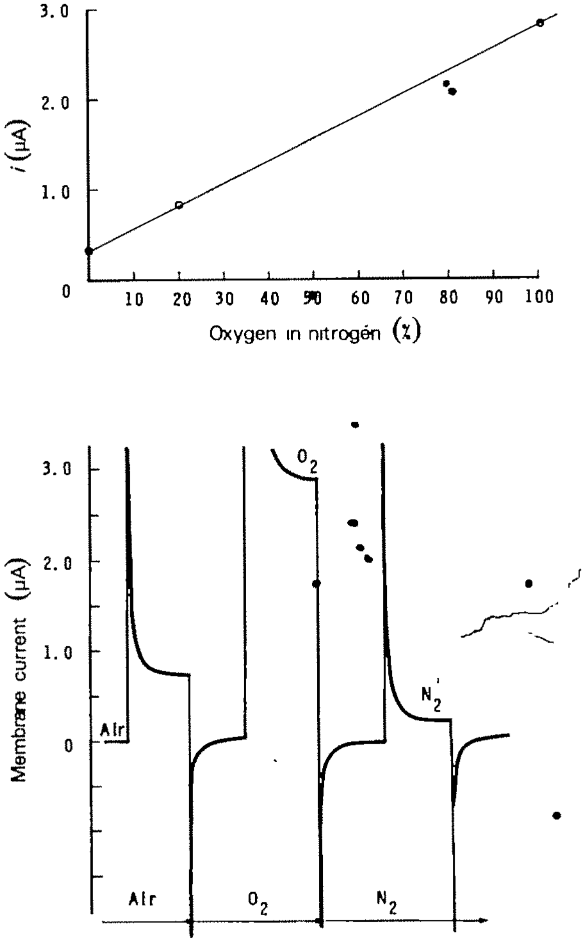

FIG. 3. Current response of metallized membrane for nitrogen, air and oxygen, when pulsed at − 0.625 V. Top: pulse current height plotted against oxygen concentration. Bottom: current–time responses.

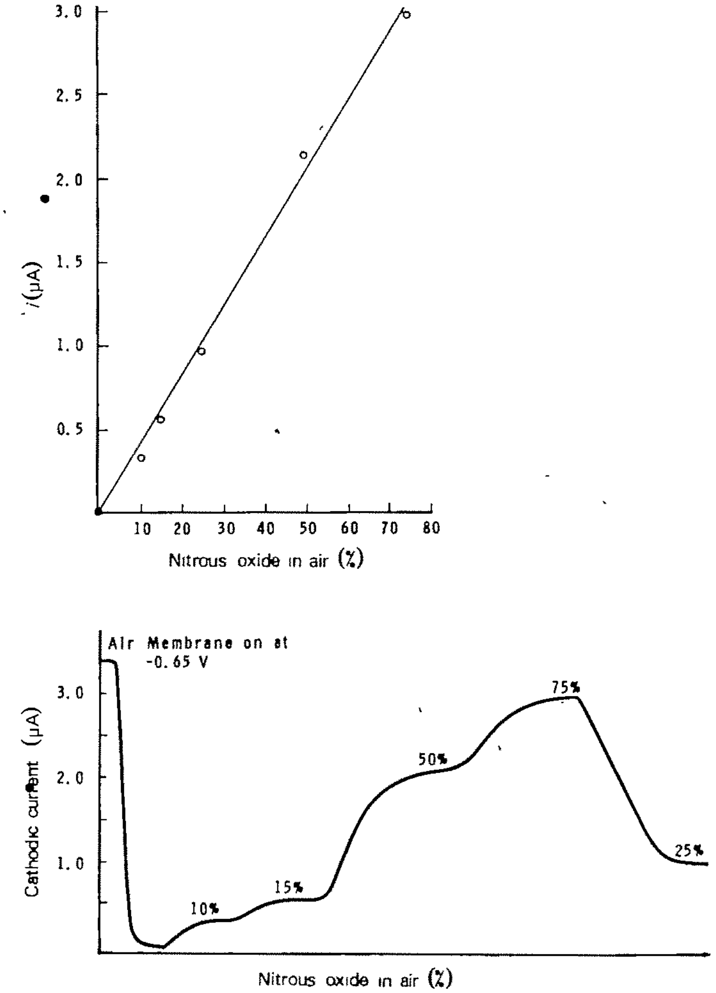

FIG. 4. Current response of inner (second) cathode, polarized at −0.65 V, to changes in nitrous oxide concentration, when the metallized membrane was polarized at −0.52 V. Top: plot of steady state inner cathode current against nitrous oxide concentration. Bottom: current responses to changes in nitrous oxide concentration. The far left of the figure shows the inner cathode current response to air, when the metallized membrane was switched from 0 V to −0.52 V.

ir, when the metallized membrane was polarized 0.52 V. The beginning of the time trace shows second cathodic current response when the membrane was at 0.0 V (that is not filtering oxygen) and when the membrane was switched to −0.52 V (that is acting as an oxygen filter). It is clear that, even though the second cathode was only polarized at −0.65 V, and was therefore not on the diffusion-limiting part of the polarographic wave for nitrous oxide on silver surfaces (Albery et al., 1978), the nitrous oxide reduction current was still proportional to nitrous oxide concentration. However, when the polarizing voltage was increased to −0.72 V, and hence much closer to the diffusion-limited part of the wave, a greatly increased reduction current was observed together with the formation of nitrogen bubbles (the nitrous oxide reduction product) on the cathode surface. Thereafter the electrode ceased to function, and it was decided to pulse the second cathode to avoid the bubble formation.

Pulsing second cathode

The nitrous oxide response of the second cathode when pulsed at −0.72 V, is shown in figure 5. The metallized membrane was polarized at −0.52 V (as in figure 4), the only difference being that the

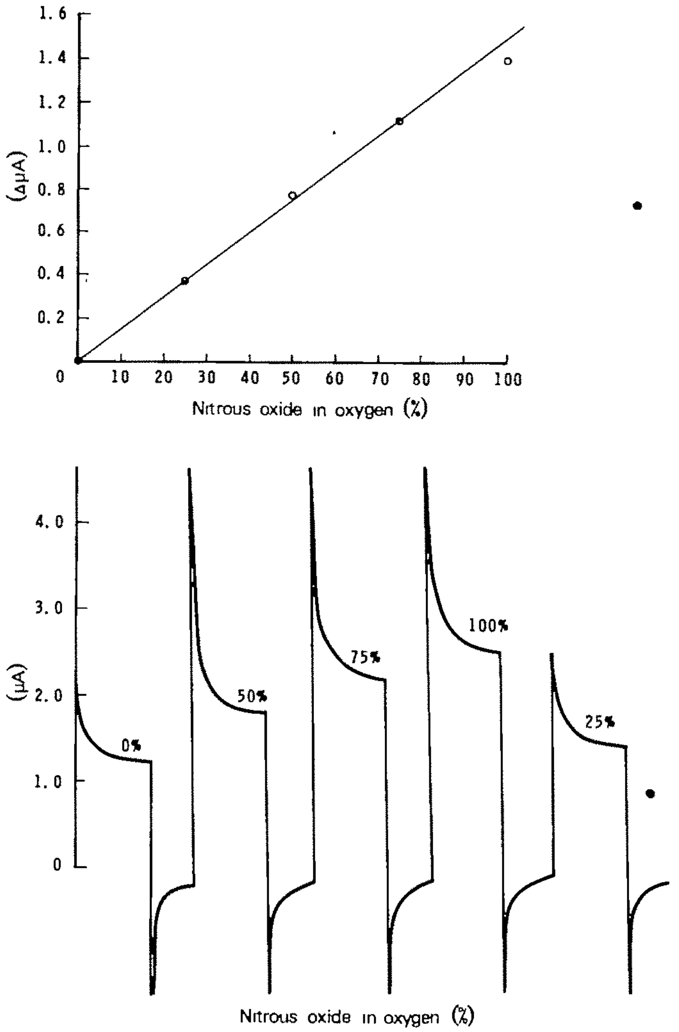

FIG. 5. Current–time responses of inner (second) cathode to pulsed polarizing voltages (0 V to −0.72 V), in the presence of different nitrous oxide concentrations, when the membrane was polarized at −0.52 V. Top: pulsed current response heights plotted against nitrous oxide concentration, for the inner (second) cathode. Bottom: actual current–time responses for different nitrous oxide concentrations.

polarizing source for the second cathode was hand-operated to produce a simple pulsing régime lasting 170 s, with a 100-s pause between pulses. Figure 5 also shows the height of the cathodic current response plotted against nitrous oxide concentration. The non linearity at 100% (v/v) nitrous oxide is undoubtably a result of the fact that the polarizing voltage was not negative enough. With hindsight it would have been better to pulse at about −1.2 V for these preliminary studies. Nevertheless, there is a gratifying linear response to nitrous oxide, and it is clear that this gas is not being filtered by the metallized membrane.

Application to halothane

The obvious next step in the development of this device would be to investigate its characteristics in the presence of halothane. The studies reported here have shown that oxygen can be filtered effectively at the metallized membrane surface; indeed, Albery and Barron (1982), in a separate study at Imperial College, London, have shown that a painted gold membrane can achieve filtering efficiencies greater than 99%. Thus, halothane and nitrous oxide would diffuse to the second cathode where they could be individually detected by pulse polarography (free from oxygen interference), in the same way that oxygen and nitrous oxide are measured in the absence of halothane (Brooks et al., 1980). Clearly, a membrane permeable to halothane (such as silicone) must be used, and the metallized layer must be formed from a metal which does not react with either nitrous oxide or halothane. We were limited in these studies to the membranes and metals which were available to us. Both silver and gold-on-silver metallized membranes would reduce halothane and we are therefore endeavouring to continue these studies with a metal which does not appear to react, such as platinum.

Our conclusions so far are:

(a) The metallized membrane acts as an effective filter for oxygen and gives a linear response to oxygen concentration.

(b) The metallized membrane will allow nitrous oxide to pass through unreduced, even when the metallized film is polarized in the oxygen reducing region.

(c) The second (inner) cathode will reduce the nitrous oxide which reaches it via the metallized membrane. A linear response is found for the nitrous oxide concentration even when the electrode is pulsed.

(d) These studies suggest that a composite "sandwich" electrode, with a metallized membrane such as platinum, which did not reduce halothane or nitrous oxide, might be able simultaneously to measure oxygen, nitrous oxide and halothane.

ACKNOWLEDGEMENT

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EINE (SANDWICH) ELEKTRODE FÜR MEHRFACH-GASANALYSE

ZUSAMMENFASSUNG

Der Prototyp einer Elektrode, aus einer metallüberzogenen membranösen "äusseren" und einer herkömmlichen "inneren" Silberscheibentkathode, die beide das gleich Elektrolyt benutzen, wird beschrieben. Ergebnisse aus Voruntersuchungen zeigen an, dass die metallisierte überzogene Membran als Sauerstofffilter funktionierten, die den Narkose-gasen wie etwa Lachgas erlaubten, die zweite Kathode (die innere) zu durchdringen, wo sie reduziert wird. Es besteht eine lineare Beziehung für die CO_2-Konzentration und dem Ström in der metallisierten überzogenen Membran und ebenso für die CO_2-Konzentration und den zweiten Kathodenström. Die Erweiterung dieser Technik um sowohl Halothan als auch Lachgas an der zweite Kathoden gleichzeitig mit O_2 am der metallisierten überzogenen Membran zu messen, wird diskutiert.

ELECTRODO COMPUESTO PARA EL ANALISIS DE GAS MULTIPLE: UN PROTOTIPO

SUMARIO

Se describe un prototipo de electrodo compuesto, constituido por una membraba metalizada "exterior" que actúa como cátodo y un disco "interior" de plata que actúa también como cátodo, compartiendo ambos el mismo electrolito. Los resultados preliminares indican que la membrana metalizada actuará cual un filtro de oxígeno, permitiendo el paso de gases anestésicos, tales como el óxido nitroso, a través del segundo cátodo (interior) en donde se les reduce. Existen relaciones lineales entre la concentración de oxígeno y la corriente de la membrana metalizada así como entre el óxido nitroso y la corriente catódica secundaria. Se discute el alcance de esta técnica para medir en el segundo cátodo el halotano y el óxido nitroso simultáneamente con el oxígeno de la membrana metalizada.

Br. J. Anaesth. (1982), 54, 689

A VERSATILE CLOSED CIRCUIT

P. BEATTY, M. F. S. WHEELER, B. KAY, W. GREER, A. T. COHEN AND J. PARKHOUSE

SUMMARY

A versatile closed circuit with new features is described. It may be used in a totally closed manner, without continuous gas inflow. As gas is absorbed from the circuit, it is replaced through a demand valve. Facilities for continuous gas input and use of a ventilator are included, and one control converts it to a non-rebreathing circuit. The circuit has excellent mechanical characteristics in all modes, and has been used extensively in routine clinical practice.

The use of closed circuit anaesthesia is frequently suggested as a method of reducing atmospheric pollution by anaesthetic gases. In practice, however, truly closed circuits are very rarely used. Normally a flow of fresh gas is fed into a circle system with carbon dioxide absorption. This gas flow invariably exceeds patient requirements and the excess gas is spilled from the circuit.

A totally closed circuit was described by Bushman and others (1977) in which the fresh gas requirement was obtained by use of a demand valve activated by sub-atmospheric pressure in a circle system after gas absorption from the circuit. One circuit configuration which utilized this principle used a self-inflating Oxford bellows in order that manual ventilation, as well as spontaneous ventilation could be undertaken. However, the mechanical characteristics of this circuit proved unsatisfactory. The work required for spontaneous ventilation when the circuit was used by conscious volunteers was too great to be tolerated for more than a few minutes.

Consequently a new circuit was designed, the characteristics of which are described here. Fresh gas flow is obtained by delivering mixtures of nitrous oxide and oxygen on demand during spontaneous ventilation or intermittent positive pressure ventilation (IPPV). If desired, a continuous low flow of oxygen may be added in a similar way to fresh gas supply in conventional closed circuits.

THE CIRCUIT

The circuit is of normal configuration (fig. 1). Continuous gas supply into the circuit passses through a low-flow oxygen meter (8). Nitrous oxide with or without oxygen may only enter the circuit as a result of the opening of demand valve (7) in response to sub-atmospheric pressure in the circuit.

The circuit has comprehensive leak-proofing to allow totally closed use, but may be switched to a non-rebreathing system by use of a single valve (3, fig. 2) mounted near the bellows. All the valves, and the soda-lime canister are mounted near the bellows for compactness, and to allow light-weight patient connections (fig. 2)

A blow off valve is provided to ensure that the pressure in the circuit can not increase to greater than 40 cm H_2O (1, fig. 1).

Bellows design

The key to achieving maximum efficiency is the design of the bellows (fig. 2). There are two opposing springs, one controlling the expansion of the bellows and the other its contraction.

The bellows bag itself is made of a light silicon rubber (Bennett Ventilator part No. 1650). It has a metal base-plate, the centre of which is connected to the two springs. The internal one (1, fig. 2) is a constant force spring (Tensator type No. BA 274), with a force calculated to be slightly greater than the weight of the bellows and base-plate. This minimizes the work involved in moving the bellows. On

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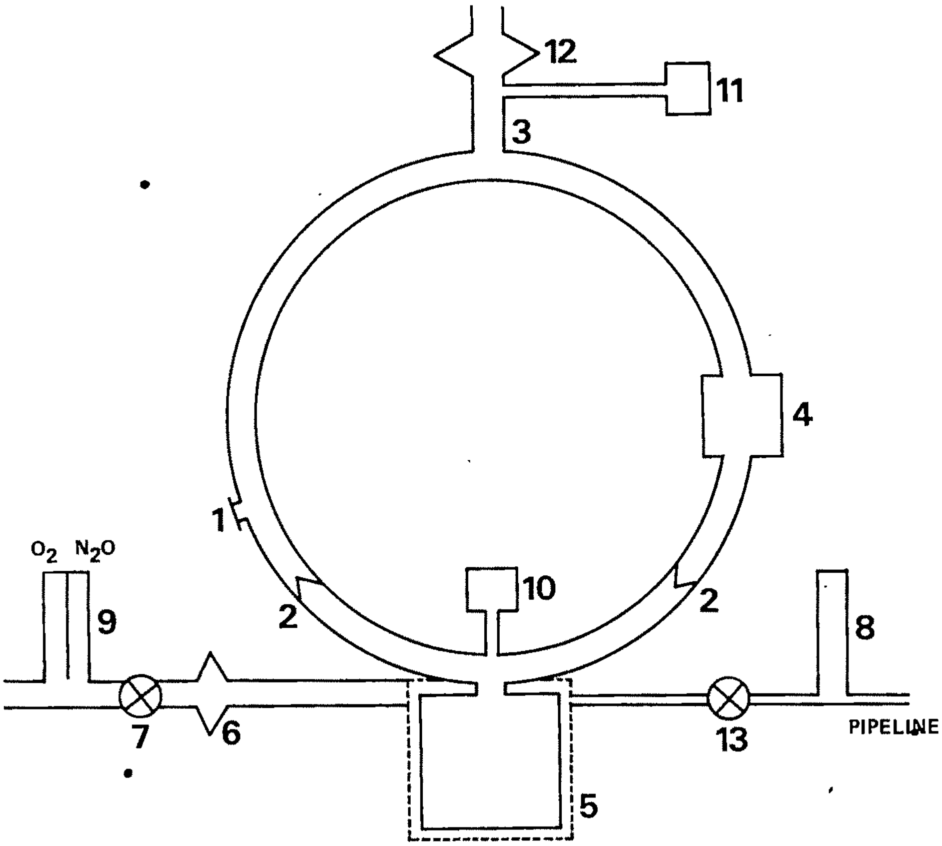

FIG. 1. Diagrammatic representation of the closed circuit, showing monitoring sites. 1 = Blow off valve; 2 = one-way valves; 3 = patient connection; 4 = soda-lime canister; 5 = bellows complex; 6 = pneumotachograph; 7 = demand valve; 8 = low-flow Rotameter; 9 = Rotameters; 10 = pressure transducer; 11 = pressure transducer; 12 = pneumotachograph; 13 = flow-limiting valve.

the outside of the bag is a spring obeying Hooke's Law (8, fig. 2). This is arranged to balance the slight lifting force on the bellows at a resting position giving the bag a volume of 700 ml. Displacement of the bag upwards from the resting position results in a restoring force which increases with increasing displacement.

Thus, during IPPV, as gas is extracted from the circuit the return of the bag to resting position will generate a sub-atmospheric pressure sufficient to open the demand valve, restoring circuit volume.

During spontaneous ventilation, as gas is absorbed from the circuit, the patient will be unable to obtain a normal inspired tidal volume from the bellows without the bellows entering an area of decreasing compliance, thereby generating a sub-atmospheric pressure sufficient to open the demand valve and restore circuit volume.

Eight stainless steel tubing rings are used in the bellows to maintain its shape during ventilation. The bellows is placed in a Penlon Ventilator casing. A Bird Mark 8 Ventilator is connected to the outlet of the casing to allow for automatic ventilation. The connection has a T-piece in it, closed by a cap for IPPV, open during spontaneous ventilation.

Demand flow inlet

The demand flow is controlled by a modified Entonox valve, which delivers to the circuit nitrous oxide or oxygen or any preset mixture as soon as the pressure on the circuit side of the valve decreases to less than -1.4 cm H_2O. The gas supply to the valve is controlled by the main Rotameters and the valve functions well if these are set to allow flows of at least 10 litre min^{-1}.

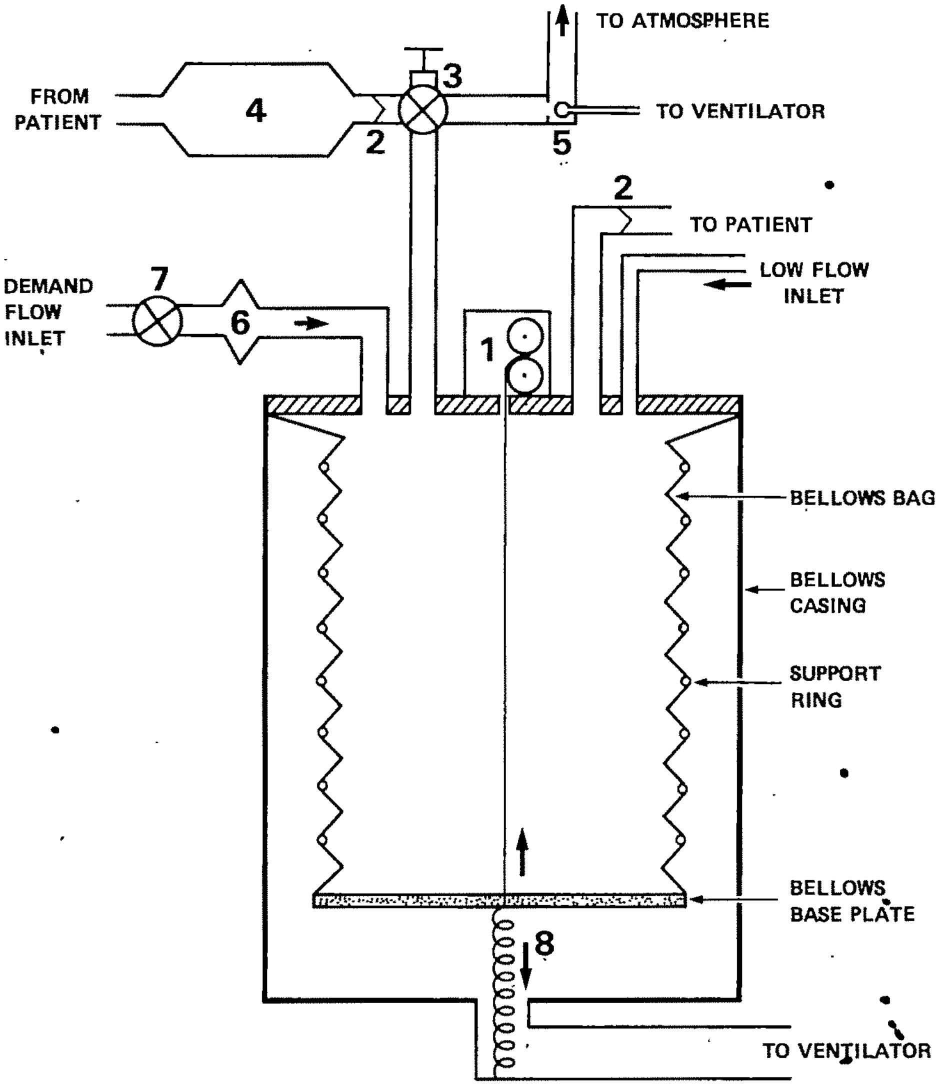

FIG. 2. Details of circuit base assembly. 1 = Constant force spring; 2 = one-way valves; 3 = circle/non-rebreathing control; 4 = soda-lime canister; 5 = ventilator controlled expiratory valve; 6 = pneumotachograph; 7 = demand valve; 8 = Hooke's law spring.

For monitoring purposes, the demand flow passes through a dry gas pneumotachograph head before entering the circuit at the top of the bellows.

Low flow oxygen inlet system

This allows oxygen to be delivered to the circuit, at a constant flow rate. The rate of flow is set using a low-range (1 litre min^{-1}) Rotameter of high accuracy (GEC Marconi Process Control type No. 1100-VAA-300).

The oxygen passes through a flow-limiting valve (13, fig. 1) preset to a maximum flow rate of 400 ml min^{-1}, and enters the closed-circuit at the top of the bellows.

Soda-lime canister

This is a Penlon canister (Type No. 52522), placed in the expiratory limb of the circuit. One of its connections is directly to the patient and the other to the top of the bellows through a flap valve (Ambu Hesse type).

Non-rebreathing facility

A non-rebreathing facility is included so that changes in circuit gas can be made rapidly. A control valve (3, fig. 2) operates so that all expired gas is vented to atmosphere or exhaust system. Fresh gas is drawn into the circuit through the demand valve during late inspiration, and as the bellows returns to rest during expiration. During non-rebreathing with IPPV the expiratory port is closed during inspiration by a Bird Pneumatic valve (No. 338).

Operation

The overall operation of the circuit can best be described by considering one breathing cycle

During IPPV, expired gases are returned to the bellows through the soda-lime absorber. The bellows expand to a constant resting position so that a shortage of volume produced by the absorption of circuit gases results in sub-atmospheric pressure which opens the demand valve. Gas flows in through the demand valve to restore resting circuit volume.

During spontaneous ventilation demand occurs at end inspiration as the bellows enters a less compliant region (see above). If a constant flow of gas is supplied through the Rotameter, the volume of gas demanded to replace the absorbed gases is reduced.

METHOD

Experiments

Simulated spontaneous ventilation. For these studies a mechanical pump was placed at the patient connection of the closed circuit to simulate spontaneous ventilation. This pump generated a sinusoidal flow, and for these experiments breathing rates of 12 and 14 per minute were simulated, with tidal volumes of 450 and 800 ml. The pump was connected to an extraction pump via a Rotameter. In this way, it was possible to extract different gas flows from the system in order to simulate uptake by the body. Extraction rates of zero, 200 and 800 ml min^{-1} were used. This could be used to illustrate the functioning of the demand action in the circuit.

Spontaneous ventilation by volunteers. Five volunteers (four male) all fit and between 20 and 30 yr and 54–75 kg were studied. They breathed into the totally closed circuit, using a mouth-piece and nose-clip. The circuit was filled with air and oxygen was supplied on demand. The volunteers breathed into the circuit for at least 15 min, and their subjective comments were recorded at the end of the experiment.

IPPV. A model lung (Manley lung ventilation performance analyser) was attached at the patient connection, and was set to have a compliance of 50 ml cm H_2O^{-1} with zero airway resistance. The performance of the circuit using IPPV was examined, as both a totally closed circuit and a non-rebreathing circuit.

Observations

The general method assessing the work of breathing in a closed circuit will be discussed by Greer (in preparation).

The pressure (P_1) at the patient connection was measured with a physiological pressure transducer (Gould, Model P50) at position 10 (fig. 1). The pressure on the circuit side of the demand valve (P_2) was monitored by a similar transducer at position 11 (fig. 1).

The flow signal at the mouth ($\dot{V}_1$) (defined positive going into the circuit) was obtained using a heated Fleisch No. 2 pneumotachograph placed in the patient connection (12, fig. 1) in conjunction with a micromanometer. The demand flow reading ($\dot{V}_2$) was collected from a dry pneumotachograph head in the demand inflow (6, fig. 1) connected to an appropriate micromanometer. Continous records of pressures and flows were obtained from an eight-channel chart recorder (Grass Polygraph) and data were gathered for subsequent processing on an Analogue Tape Recorder (Tandberg Model 1600 S3).

The pressure and flow transducers were calibrated against a water manometer and certified Rotameters, respectively, before each set of experiments were carried out, and the calibrated signals read on to magnetic tape at the beginning of the experimental session. During tests selected sections of pressure and flow data were recorded for the various experiments. These sections were selected after time had been allowed to reach stability of circuit behaviour.

Data analysis

This information was transferred directly into a Nova computer (Data General) and the data processed using programs developed in this department. The routines used synchronize the different sets of data to allow study of each breath independently. The programs derive volumes by integrating flow–time curves. This numerical information was then plotted as a variety of graphs including flow–pressure loops, volume–pressure loops and volume–differential pressure loops. This method of analysis allows the allocation of various elements of the total work involved to specific components of the circuit and connections to the circuit.

RESULTS

Closed circuit, spontaneous ventilation

For assessing the mechanisms of the circuit, the most important readings obtained are those from the patient connection. Figure 3 illustrates the changes in pressure, flow and volume with the time at this point, obtained in one volunteer using a closed circuit. Figure 4 illustrates the pressure–volume loop for one breathing cycle derived from these. By calculating areas A_1, A_2, A_3 and A_4, the work done in the various parts of the cycle can be found. The sum of the whole equals the total work involved: A_1+A_2 is the work in inspiration, A_3+A_4, the work in expiration. The work done by the patient is A_2+A_4 and that by the bellows A_1+A_3.

Table I lists the results obtained in the volunteer studies and also gives the results from a single experiment with simulated spontaneous breathing (12 cycles per min, 450 ml tidal volume, extraction rate of 200 ml min^{-1}). Results using faster rates and larger volumes did not vary in form.

Figure 5 illustrates volume change against the pressure differential between P_2 and P_1 (inside the bellows and at the patient connection). This curve allows calculation of work done in overcoming circuit resistance. A_5 gives the work involved in inspiration and A_6 the expiratory component. These are also included in table I.

Figure 6 illustrates the pressure changes occurring in the bellows (P_2) during a respiratory cycle, together with flow pattern in the demand flow inlet ($\dot{V}_2$) and derived volume entering the circuit. The function of the demand valve is seen, opening at -1.4 cm H_2O, reflecting some hysteresis in the

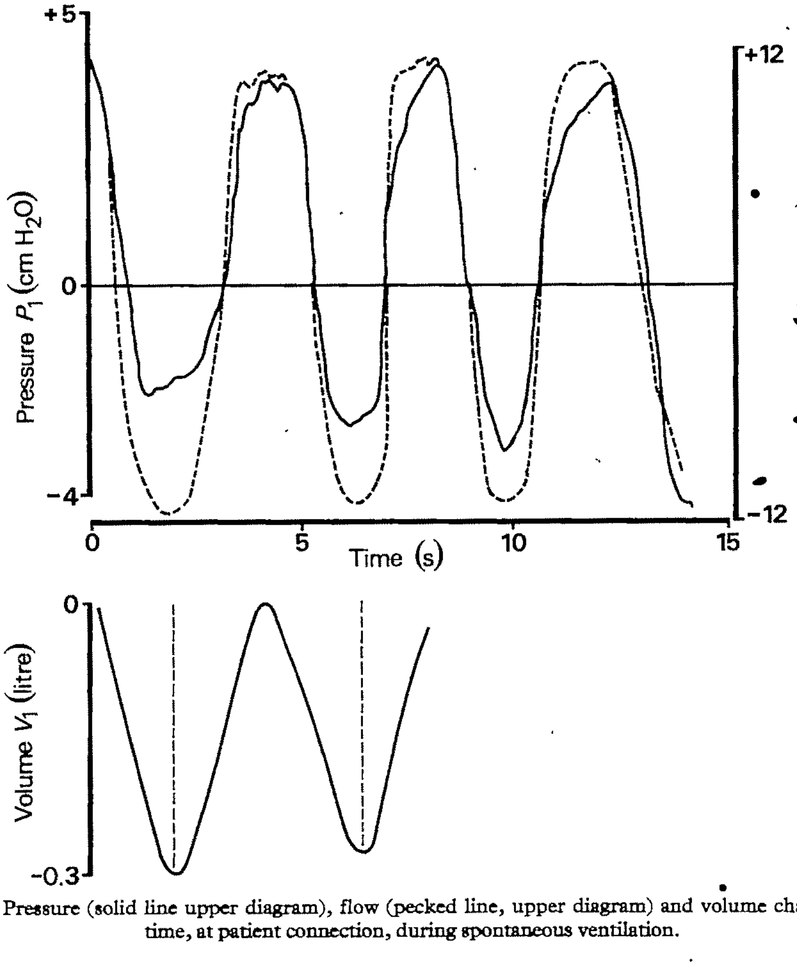

FIG. 3. Pressure (solid line upper diagram), flow (pecked line, upper diagram) and volume changes with time, at patient connection, during spontaneous ventilation.

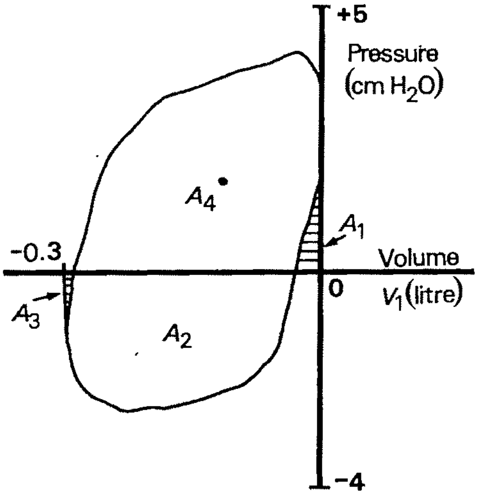

FIG. 4. Pressure–volume loop, obtained at the patient connection during spontaneous ventilation. The work done during different parts of the breathing cycle is computed from the areas A_1–A_4.

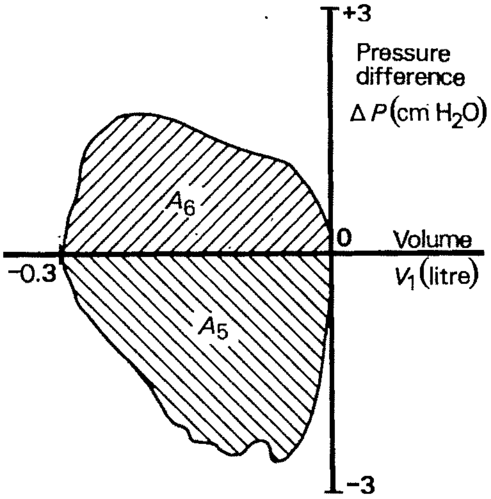

FIG. 5. Volunteer studies. Pressure difference across circuit (bellows to patient connection) plotted against integrated flow rate at patient connection, in a volunteer study. A_5 indicates work done against inspiratory resistance, A_6 work against expiratory resistance.

valve. In this case the delivery of gas lasts for 1.5 s and the volume delivered is 46 ml. When simulated spontaneous ventilation without gas extraction was used, no gas was demanded into the system, indicating highly effective leak-proofing.

Non-rebreathing system

Figure 7 illustrates a pressure–flow loop at the patient connection (P_1 *v.* $\dot{V}_1$), before and after switching the circuit from closed to non-rebreathing during simulated spontaneous ventilation (12 cycles per min, 450 ml tidal volume, 200 ml min^{-1} extraction). The loop obtained during non-rebreathing was similar to that obtained using a Mapleson A system (Smith, 1961).

The work involved in these conditions is very similar, whether the circuit is closed, or non-rebreathing. In the latter case, extra work involved was 137 mJ per cycle, with the bellows contributing a negligible amount. The inspiratory work (116 mJ

TABLE I. *Closed circuit studies with spontaneous ventilation. All units of work in mJ*

	Volunteers						
	A	B	C	D	E	Mean value	Simulation
Breaths per minute	15	13	7	10	15	12	12
Extra work per breathing cycle	101	145	189	141	188	153	113
Work done in inspiration	42	58	98	56	83	68	71
Work done in expiration	59	87	91	85	105	85	42
Work done by bellows	2	3	11	16	7	8	3
Work done by patient	99	142	178	125	181	145	110
Total work used in breathing against circuit resistance	57	88	83	86	117	86	48
Inspiratory work used in breathing against circuit resistance	26	54	58	47	70	51	42
Expiratory work used in breathing against circuit resistance	31	34	25	39	47	35	6
Mean tidal volume (ml)	266	334	576	489	259	385	450

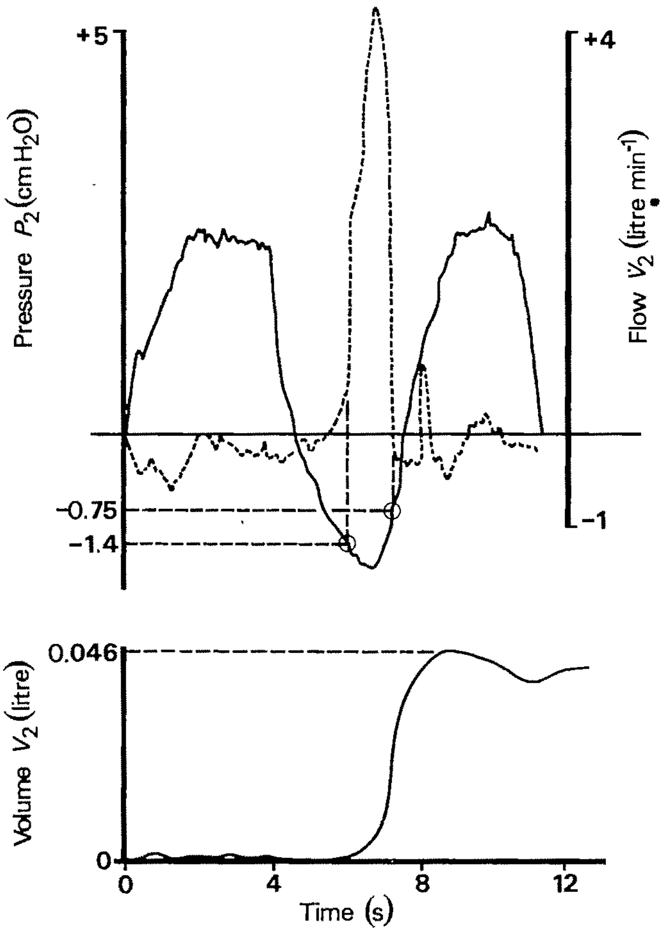

FIG. 6. Pressure at bellows (solid line upper diagram), flow at demand inlet (pecked line upper diagram and integrated flow (volume) at demand inlet (lower diagram) *v.* time. From the volume trace we can see that 46 ml of oxygen are delivered per breath (therefore 322 ml min^{-1}).

per cycle) is relatively much greater than during closed circuit use, reflecting a higher (smaller volume) end-expiratory position of the bellows, with the work of inspiration occurring against an increased extension of the Hooke's law spring.

IPPV

During IPPV the circuit behaved as expected, in line with previous experimental experience. Pressures, flows and volumes reflected the ventilator settings. Inspiratory work is of course irrelevant, but is similar to that required for spontaneous ventilation. Expiratory work was very small indeed, varying with tidal volumes used. With a tidal volume of 450 ml, total expiratory work was 35 mJ, of which 21 mJ was contributed by the bellows action.

Clinical experience

The circuit as described is mounted on a trolley with the Bird ventilator fixed to the top. The bank of precision Rotameters is mounted at the rear. Pipeline oxygen and nitrous oxide are fed to the back of the trolley with back-up cylinders and reducing valves. A control for non-rebreathing mode or closed circuit use is positioned at the front of the trolley.

The circuit is initially flushed in the non-rebreathing mode with a mixture determined by the setting of the Rotameters, which in the closed circuit mode supply the demand valve. Thus the demand valve can be supplied with a predetermined mixture of nitrous oxide and oxygen, oxygen alone, or nitrous oxide alone. In the last case a low flow of

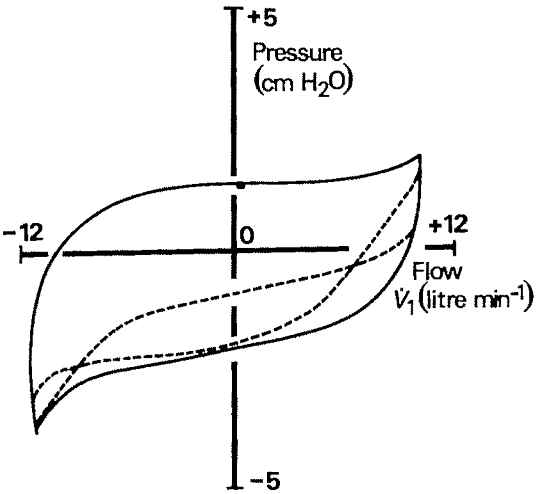

FIG. 7. Flow–pressure loop for totally closed circuit (solid line), and semi-closed circuit (pecked line). Conditions: tidal volume 450 ml, 12 b.p.m. and 200 ml of gas extracted per min.

oxygen is fed into the circuit from the special low flow oxygen Rotameter.

Unless the nitrogen content of the functional residual capacity (FRC) is previously eliminated, within minutes after connection the closed circuit will contain an appreciable concentration of nitrogen. By temporarily selecting the non-rebreathing mode, this nitrogen can be flushed out of the system. We have found the most effective flushing regimen to be 20 breaths within the first 3 min.

Our clinical experience is similar to that of Barton and Nunn (1975) in that, after FRC washout, circuit nitrogen build-up is not a problem. However, to keep the concentration less that 5%, we would recommend flushing for 10 breaths every 30 min.

The volume of the circuit in addition to the patient's FRC is approximately 8 litre. This large volume is such that changes in concentration occur slowly, and not surprisingly we have not found any difficulty maintaining steady circuit gas concentrations.

We have used this circuit in clinical practice for nearly 2 yr. Routine unselected use during a general surgical operating list has shown that after initial familiarization it is easy to use with either spontaneous ventilation or IPPV.

More than 200 patients aged between 17 and 81 yr and mostly undergoing major surgery, have been anaesthetized using the circuit. Duration of anaesthesia in these cases ranged from 40 min to 6.5 h.

In the majority of patients (more than 70%) anaesthesia was maintained with 60–75% nitrous oxide in oxygen, with narcotic analgesic supplement, muscle paralysis and IPPV, although the circuit was switched to spontaneous ventilation mode after antagonism of the muscle relaxant. In the minority of patients, including all those in whom spontaneous ventilation was allowed throughout, the circuit was used to deliver oxygen only, with in-circuit vaporization of halothane or enflurane.

When we have used nitrous oxide and oxygen alone in the circuit, we have used one of two basic methods. After a short non-rebreathing period we set a mixture of nitrous oxide and oxygen to be delivered by the demand valve, adjusting the concentrations as required. Usually however, we have supplied a small constant flow of oxygen (the estimated oxygen uptake for the patient), and supplied only nitrous oxide on demand.

When nitrous oxide is being used in the circuit, a

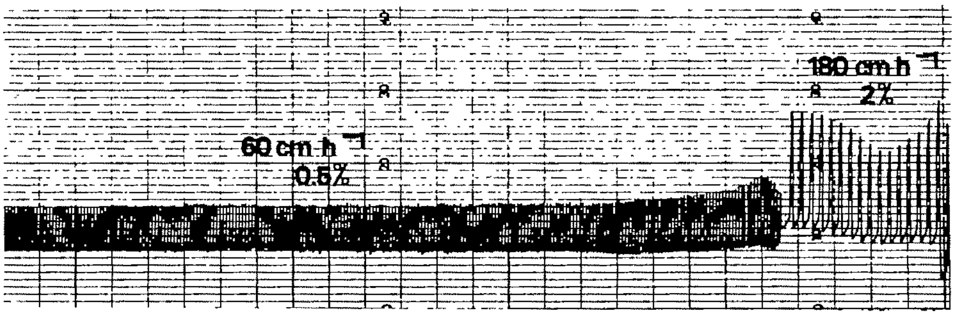

FIG. 8. Halothane concentrations measured at Y-connector of patient undergoing anaesthesia on the closed circuit (IPPV). The first section of the trace (paper speed 180 cm h^{-1}) shows effect of setting the vaporizer to the 2% mark for 17 breaths. Paper speed was then reduced to 60 cm h^{-1} concurrently with the vaporizer being reset to 0.5%. The trace remained stable, with end-expired halothane of 0.8% to the end of anaesthesia, which was approximately 1 h.

simple oxygen analyser can reassure the anaesthetist that an hypoxic mixture is not being delivered, and use of our flushing regimen, ensures that nitrous oxide concentrations are maintained.

When the circuit is being used to deliver oxygen and halothane or enflurane mixtures, we have used a low resistance draw-over vaporizer (Oxford Miniature Vaporizer) in circuit (not recommended by the makers) to produce remarkably consistent halothane concentrations, even with IPPV. Figure 8 shows that a short period of overpressure at the onset of anaesthesia helps produce these stable concentrations.

Circuit halothane concentrations can be readily monitored using an appropriate monitor. We use the EMMA (Engstrom Medical AB). Oxygen is usually admitted on demand, but a low constant flow may be supplied to reduce demand function if this is preferred.

Details of the performance of this circuit, with nitrous oxide–oxygen, and oxygen–volatile anaesthetic mixtures will be reported elsewhere. At present, when using an in-circuit Oxford Miniature Vaporizer, it is considered essential to monitor volatile anaesthetic concentrations continously.

The circuit has proved to be effective, reliable and versatile in routine clinical practice. We have only used the techniques outlined above, but other combinations are possible. There has been no instance of failure of any part of the circuit, nor has its use ever led to dangerous circumstances.

CONCLUSIONS

The circuit described has been shown to be an effective, versatile circuit, capable of being used in a totally closed or non-rebreathing manner. The analysis of its mechanical characteristics shows the system to be extremely light in action in all circumstances, a fact confirmed by opinions of the volunteers studied. This favourable impression of the function of this circuit has been reinforced by extensive clinical use. The ability to use a totally closed circuit has also facilitated clinical studies of gas uptake during anaesthesia. Subsequent experience has also confirmed that the circuit has remained substantially leak-free in normal clinical use, rendering totally closed circuit anaesthesia without continuous gas inflow a practical possibility for the future.

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UN CIRCUIT FERME ADAPTABLE

RESUME

Il s'agit de la description d'un circuit fermé adaptable présentant quelques traits nouveaux. Il peut être utilisé comme un circuit complètement fermé, sans arrivée continue de gaz. Au fur et à mesure que le gaz est absorbé hors du circuit, il est remplacé par l'intermédiaire d'une valve d'admission. Sa structure comprend des facilités pour admettre les gaz de façon continue et pour utiliser un respirateur, et un contrôle le transforme en circuit sans "rebreathing". Ce circuit a d'excellentes caractéristiques mécaniques dans tous les modes et a été largement utilisé en pratique clinique courante.

EIN WANDELBARES GESCHLOSSENES KREISSYSTEM

ZUSAMMENFASSUNG

Eine wandelbares geschlossenes Kreissystem mit neuen Eigenschaften wird beschrieben. Es kann total geschlossen verwendet werden ohne kontinuierlichen Gaszuström, wenn Gas aus dem kreissystem absorbiert ist, wird es durch ein Bedarfsventil ersetzt. Einrichtungen fur kontinuierlichen Gaszufuhr und Benutzung einer Pumpe sind eingebaut, und ein Regler verwandelt es in ein Kreissystem in dem nicht zuruckgeatmet wird. Das System hat ausgezeichnete mechanische Eingeschaften in allen Verwendungsarten und wurde ausschliesslich im klinische Routinebetrieb verwendet.

UN CIRCUITO CERRADO VERSATIL

SUMARIO

Se describe un circuito cerrado versátil que presenta características nuevas. Puede usarse cual circuito totalmente cerrado sin entrada continua de gas. A medida que el circuito absorbe gas, éste se repone mediante una válvula de demanda. Se incluyen los medios para la entrada continua de gas y el uso de un ventilador, al tiempo que un control lo convierte en un circuito que impide su respiración de nuevo. El circuito presenta características mecánicas excelentes en todas sus modálidadas y se ha usado extensivamente en la práctica clínica de rutina.

Br. J. Anaesth. (1982), **54**, 699

CORRESPONDENCE

PHARMACOKINETICS OF ORG NC45

Sir,—In recent years there has been an ever increasing number of articles on the pharmacokinetics and pharmacodynamics of muscle relaxants. Despite this deluge of mathematical models, there are some who view many of these studies as interesting mental exercises, but insist that they shouldn't be taken too seriously (Feldman, 1981). A paper by van der Veen and Bencini (1980) gives further ammunition to the sceptics.

In table III, the authors average data from four subjects and tell us (to give just one example) that $T_{\frac{1}{2}}^{\alpha}$ is 3.9 min and α is $0.25\,\text{min}^{-1}$. Since α is the reciprocal of the time constant, if α is correct then $T_{\frac{1}{2}}^{\alpha}$ is really 2.77 min. If $T_{\frac{1}{2}}^{\alpha}$ is actually 3.9 min, then $\alpha = 0.18\,\text{min}^{-1}$. If the distribution half-life was calculated first for each patient, and the parameter α was derived from the former data, then pooling the values of α is not only useless, but it is misleading as well. If the averaged values of α and β are used to construct a mathematical model, then the resultant analyses will show more rapid decay of plasma concentrations than actually occurs. If, as I suspect was the case, the values of α and β came first, the average half-lives of α and β must be derived from the mean values of α and β and not from averaging the calculated half-lives of each individual.

The computer-fitted curves derived from these four patients relating the plasma concentration of Org NC 45 and neuromuscular block look very pretty but when the standard error of the mean for $T_{\frac{1}{2}}^{\alpha}$ is plus or minus 1.4 min and the mean is less than 4 min, one wonders if such handsome graphics can really be justified. Certainly, they imply a degree of precision that doesn't exist in fact.

The author's concluding statement: "The combination of the kinetic and dynamic models described here should allow predictions to be made ..." has to be taken, I'm afraid, with considerable reservation.

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van der Veen, F., and Bencini, A. (1980). Pharmacokinetics and pharmacodynamics of Org NC 45 in man. *Br. J. Anaesth.*, 52, 37S.

Sir,—We agree with Dr Kopman that one can argue about the best way of averaging individual kinetic and dynamic parameters. In our opinion, the best way of handling this problem was suggested by Chiou in a number of publications (Chiou, 1979, 1980).

We have not suggested, however, which average (arithmetic, harmonic, geometric, modus, median, etc.) should be used as a basis for predictions. It is common knowledge amongst those who are used to applying pharmacokinetic principles that any average may be given, provided it is stated which average was used and provided the correct average is used for predictions or for "mean curves". It is quite clear from the tables we have given that we used the arithmetic mean. It should also be clear that, when trying to make predictions, one is *not* free to take the arithmetic mean of every parameter. It is quite usual that a half-life calculated from the arithmetic mean of rate constants differs from the arithmetic mean of the individual half-lives; we would be surprised if it was not the case. Similar problems arise when using distribution volumes and clearances. For simulation purposes, the harmonic mean should be used for the volume of distribution, the clearance and the half-lives. Another example is found in areas of plasma concentration *v.* time curves and the rate constants: here it is the arithmetic mean that should be used.

With respect to the degree of precision with which parameters are estimated, it is not unusual to find relatively large inter-individual differences. It is not commonly known that, even in the case of estimating individual parameters from empirical data, the standard error of the parameter estimate is usually somewhere between 5 and 50% even for good empirical data. Nevertheless, it is acceptable to use average kinetic and dynamic parameters to predict "trends and tendencies" and to establish differences or similarities with other drugs of the same type.

Since the publication of the manuscript under discussion the validity of the combined pharmacokinetic/pharmacodynamic model with respect to its ability to make predictions has been challenged experimentally. Good agreement was found between experimental data (plasma concentration and effect) and predicted values in single and double infusion studies.

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REFERENCES

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—— (1980). New calculation method of mean total body clearance of drugs and its application to dosage regimens. *J. Pharmaceut. Sci.*, 69, 90.

INTRATHECAL MORPHINE IN TETANUS

Sir,—Tetanus toxin acts on internuncial neurones and increases polysynaptic reflexes in the spinal cord (Kryzhanovsky, 1965). Intrathecally applied narcotics provide pain relief by acting on opiate receptors in the synaptic junction of the substansia gelatinosa of the dorsal horn, the region which modulates the nociceptive input in the spinal cord (Yaksh and Rudy, 1976).

We are accustomed to using morphine i.v. in the sedation of patients with tetanus to facilitate controlled ventilation.

We considered that intrathecal application of morphine might have some beneficial effect in tetanus and now report two patients treated in this way.

Patient I

A 45-year-old woman had received our standard treatment for tetanus for 8 days. Sedation was with i.v. morphine, chlorpromazine and a thiopentone infusion; an antibiotic was given, and muscle relaxants were administered to enable ventilatory therapy. We gave 10 mg of morphine hydrochloride in saline 10 ml intrathecally and the use of sedatives and muscle relaxant was ceased. Subsequently, the patient did not need any other sedative or muscle relaxant for 16 h. On the following day, intrathecal morphine was given for the second time and it acted as before for 11 h. A third morphine administration on the next day lasted only 3.5 h. The patient recovered 28 days later. Arterial pressure and heart rate values before and after each intrathecal morphine injection are in table I.

Patient II

A 27-year-old woman had suffered criminal abortion 10 days previously. She had rigidity and generalized tonic contractions. She was sedated with morphine, chlorpromazine and a thiopentone infusion and muscle relaxants were given to allow artificial ventilation of the lungs.

On the 3rd day of treatment, intrathecal morphine (10 mg in saline 10 ml) was given and other drug treatment was discontinued. Following intrathecal morphine injection the patient exhibited no spontaneous movements for 15 h. On the next day the same treatment was applied and its effect lasted 14 h, but the effect of the third injection lasted only 3.5 h and the fourth injection of morphine 20 mg was ineffective. The patient died 5 days later from pulmonary failure. The cardiovascular data are in table I.

We think that the intrathecal injection of morphine can provide satisfactory sedation in patients and avoids the need for muscle relaxant drugs during artificial ventilation.

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TABLE I. *Cardiovascular data*

Injection of i.t. morphine	Duration of action (h)	Arterial pressure (mm Hg) Before	Arterial pressure (mm Hg) After	Heart rate (beat min^{-1}) Before	Heart rate (beat min^{-1}) After
Patient I					
1	16	90/50	60/40	110	70
2	11	110/60	70/40	82	72
3	3.5	100/55	70/40	75	78
Patient II					
1	15	90/50	80/45	110	98
2	14	110/60	90/50	126	90
3	3.5	110/60	110/60	122	108
4	Nil	110/60	110/60	118	120

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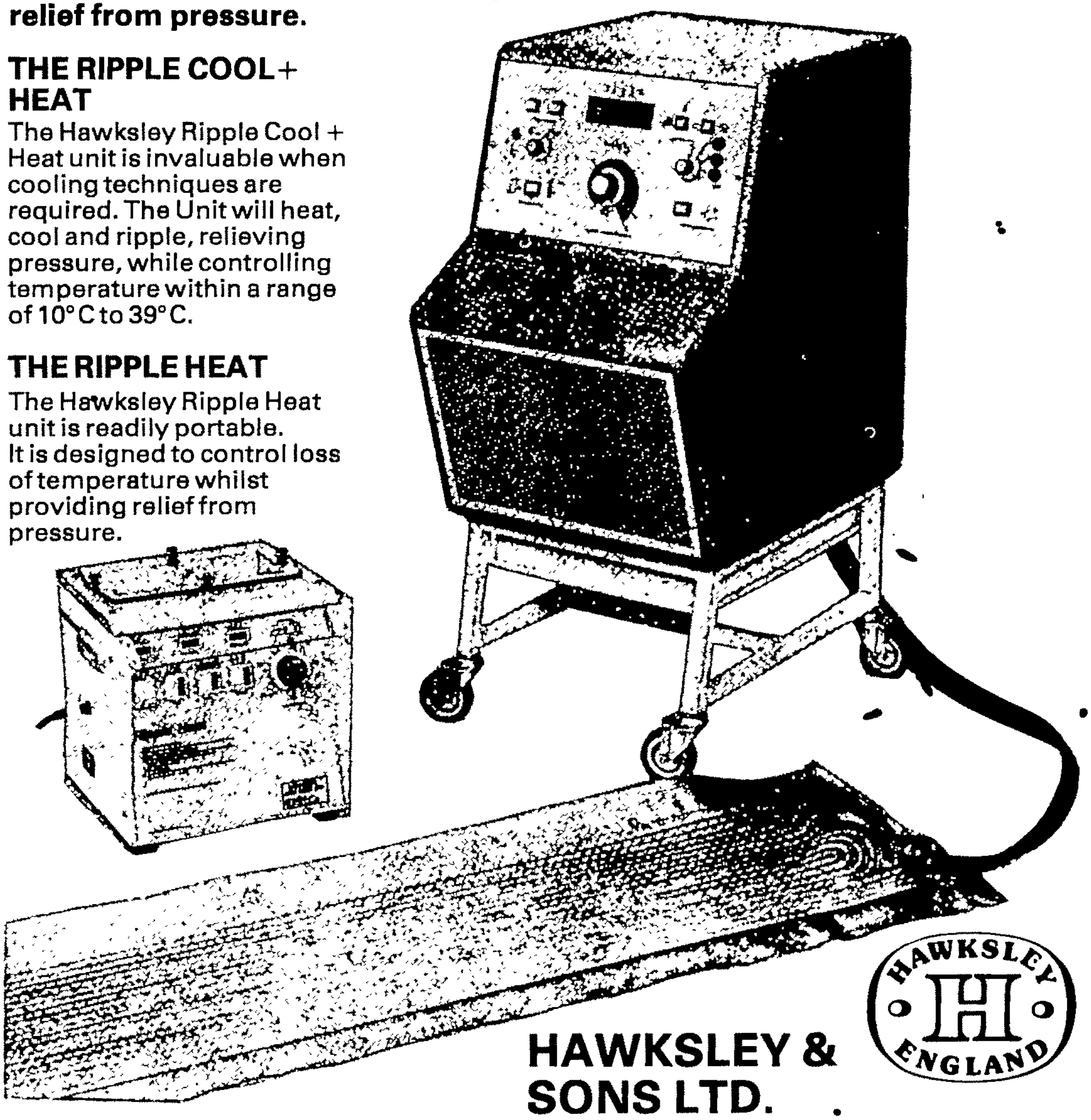

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